Joel Rodriguez-Saldana
Editor

The Diabetes Textbook

Clinical Principles, Patient Management and Public Health Issues

Second Edition

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Preface to the Second Edition

For Andy and Ashley, lighthouses of my life

The first edition of *The Diabetes Textbook* was the result of more than three decades of endeavors in outpatient diabetes management, starting with the creation of a diabetes clinic in a public hospital in Mexico City in 1990. Shortly afterwards, we met Dr. Donnell Etzwiler and his colleagues from the International Diabetes Center in Minneapolis. Don was an advocate of structured diabetes care using a scientifically based, cost-effective and patient-centered approach [1]. He was also aware of the need to improve the quality of diabetes care based on principles established by Shewhart, Deming, Juran, and many other brilliant minds in the history of quality in industry. Don was a highlight in our efforts to develop and implement an outpatient diabetes model that has benefited thousands of people with diabetes, mostly from undeserved communities. Starting in 1991, we have presented an international diabetes conference in which we have assembled a large faculty of experts from all over the world, including basic science, public health, and clinical management. Many of them became longtime friends, collaborators of *The Diabetes Textbook*, and strong supporters of its creation. We have come to understand that communication, collaboration, and hard work are crucial to confront "the largest epidemic in human history" in the words of Professor Paul Zimmet [2]. The COVID-19 pandemic has confirmed the crucial link of globalization and social determinants of health in outcomes and prognosis; diabetes is a clear example of the persisting consequences of health disparities [3].

The second edition of *The Diabetes Textbook* recognizes the importance of multidisciplinary management. I am extremely grateful for the contributions and enthusiasm of almost two hundred experts from five continents. Their expertise in the most diverse professional areas reflects the complexities of diabetes care and the multiple needs for its management. New chapters have increased the scope and enriched the previous edition, and comprehensive updates have been carried out in the original version. All the coauthors are kindly and forever recognized, but special thanks are directed to Sanjay Kalra and Maggie Powers, and very especially to Victoria Serhiyenko, who in the midst of a national tragedy provided her invaluable support. Above all, this book is devoted to persons with diabetes and their families [1]. The burden on suffering continues to be huge, and every day we honor our commitment to support them to achieve a successful life with diabetes.

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2023

Joel Rodriguez-Saldana

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Preface: A New Disease?

1

Joel Rodriguez-Saldana

At the Scientific Sessions of the American Diabetes Association in 1992, Professor Gian Franco Bottazzo delivered the Banting Lecture, in which he announced that diabetes was "a new disease," based on criteria originally described by Mirko D. Grmek in his classical book about the history of AIDS:

Criteria to define a new disease [1, 2]:

1. Previously nonexistent
2. Previously existent but rare
3. Only occurring in regions
4. Only occurring in animals

Grmek reflected that "a disease can appear to be new in at least five different settings: (1) when it already existed but was unrecognized as a clinical entity; (2) if it already existed, but did not appear until changes occurred in its manifestations; (3) if it did not exist in one region of the world; (4) if it did not exist in humans; (5) if it is absolutely new [2, p. 108]". Diabetes has been recognized as a clinical entity since early times, but its magnitude worldwide and its phenotype have remarkably changed over the last few decades.

The ancient history of diabetes started in Egypt, Asia, and Arabia 3500 years ago [3–5]. The first recorded description appeared in 1552 BC in the Ebers papyrus, the oldest and most complete medical record from ancient Egypt. In the second century AD, Arateus from Cappadocia in Greece coined the term "diabetes" to describe polyuria as the most common symptom of the disease, "a melting down of the flesh and limbs into urine," and he also gave the most detailed account of diabetes ever published (Bliss, Galmer). In the fifth to sixth centuries AD, Sushruta and Charuka in India described the sweetness of urine, the use of ants to diagnose the urine of a person with diabetes, and the distinction of two types of diabetes, one affecting thin, young individuals and another type in the obese elderly (Galmer).

Reports of persons with diabetes were scarce in the ancient period, but despite arising worldwide interest, Hippocrates made no mention of it, and Galen regarded diabetes as a kidney disease ("diarrhea of the urine") associated with "dipsakos" (violent thirst) [5]. In those days, Galen admitted that it was a very rare disease, which he had only observed twice, but at the same time proposed tasting the urine as probably the first diagnostic method in the world (Tattersall). The contributions to the study of diabetes from Avicenna in Arabia are multiple: he gave an accurate description of its clinical features; he listed some of its vascular and infectious complications, including sexual dysfunction, gangrene, carbuncles, and tuberculosis; he noted that when the urine evaporated, it left a residue like honey; and he recommended treatments based on mixtures of seeds with mild hypoglycemic activity [3]. Advances in the diagnosis of diabetes started to appear centuries later in Europe, including the description of a powderlike deposition in the urine of diabetic persons by Paracelsus in the sixteenth century, the sweet taste of urine in people with diabetes by Thomas Willis in the seventeenth century, the measurement of glucose in urine by Dobson in the eighteenth century, the description of excess sugar in the blood and urine by Rollo, who first used the term "mellitus" as the Latin and Greek root for honey, and the identification of glucose as the type of sugar in the blood and urine of people with diabetes in the nineteenth century by Chevreuil [3–6].

Diabetes was still a rare disease in this period, and like almost all other patients, people with diabetes received more harm than good from doctors' orders, including bleeding, blistering, and doping with opium, which was still in use in the early twentieth century and was very difficult to discontinue (Bliss). In the absence of effective glucose-lowering medications, therapeutic interventions were limited to diet, exercise, and "behavior," including eating large quantities of sugar (Piorry), reducing food intake and exercising (Bouchardat), starvation dieting (Allen), or specific types of carbohydrates (von Noorden), and even isolating patients under lock and key to obtain "sugar freedom" (Cantoni and

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Naunyn) (Bliss, Galmer, Hurley, Tattersall). Despite all these efforts, life expectancy for people with diabetes was very low, especially in children.

The etiology of diabetes started to be pursued in the nineteenth century. Proposed factors were multiple and disparate, including "grief," "chills," and "excess of venery" (Elliotson), "exposure to cold," "rheumatism and gout," "mental anxiety and distress" (Prout), "sexual excess," and "hereditary predisposition." Based on his assumption that sugar was formed in the stomach from vegetables, Rollo made one of the first proposals of a diabetic diet in which greens were eliminated and consisted mostly of animal food, emetics, ammonia, and narcotics [4] (Tattersall). A "thunderbolt" in the physiological world disclaiming these assumptions occurred when Claude Bernard showed that blood glucose levels are regulated not just by the absorption of dietary carbohydrates but also by the liver from glucose and non-glucose precursors, its storage as glycogen, and the involvement of the central nervous system in controlling blood glucose concentration [4]. In persons with diabetes, he stressed that the cause of the disease was a disequilibrium between sugar formation and disintegration.

The site of diabetes. Early speculations about the source of diabetes located the disease in the stomach, frequently in the kidneys, or systemically as a derangement of the central or autonomic nervous system [3–5] (Farmer, Hurley, Tattersall). Originally considered a supportive cushion in which the surrounding visceral organs rested, anatomic dissection allowed the identification of its ducts and their role in digestion [5]. Advances in "the experimental period in the history of diabetes" included the microscopic description of the pancreas by Langerhans and the endocrine function of the islets by Laguesse [3]. Cawley was the first to suggest a relationship between the pancreas and diabetes, and Minkowski and Mering confirmed the role of the pancreas in diabetes when they showed that pancreatectomized dogs developed "real permanent diabetes, which corresponded in every detail to the most severe form of the disease in man," and which could be reversed by subcutaneous implantation of pancreatic fragments [4, 5]. The race to isolate the hypothesized glucose-regulating hormone which in 1909 was named insulin by Jean de Meyer (Tattersall) was on. Between 1900 and 1921, at least five investigators came close to its discovery, including Nicholai Paulescu from Romania, who described a pancreatic extract that cured diabetes in pancreatectomized dogs in 1916, but for lack of resources, he could not produce it in large quantities.

The Discovery of Insulin and the Start of a New Era. The discovery and purification of insulin by Banting and Best from bovine pancreases with the support of MacLeod and Collip, and the first injection on a human being on January 11, 1922, "was (and still is) one of the most dramatic events in the history of the treatment of the disease (Bliss)," the crowning event of the race started by Mering and Minkowski in 1899 [5, 6] (Tattersall). At 2:00 AM on October 31, 1920, Frederick G. Banting, a surgeon practicing in Canada, conceived the idea to isolate the internal secretion of the pancreas. The following week, he met with John JR McLeod in Toronto to develop a research plan. By August 1921, Banting and his student assistant Charles H Best had prepared an effective extract from a canine pancreas, and in January 1922, James B Collip isolated insulin that was sufficiently pure for human use; for the first time in January 1922, Leonard Thompson, a 14-year-old with type 1 diabetes[7]. On October 25, 1923, Banting and McLeod received the Nobel Prize in Physiology or Medicine for the discovery of insulin, which started a new era of hope for people with diabetes [7].

Therapeutic use of insulin quickly spread around the world and became a remarkable example of the rapid translation of basic science into a benefit for patients [6]. Unfortunately and beyond its landmark achievement, the discovery of insulin has still not solved the problem of diabetes (Bliss). Initially, there were expectations that insulin would allow the islets of Langerhans to recover completely, so diabetes was cured [8]. The burden of microvascular complications was not recognized until the late 1930s and early 1940s in persons who had been saved by insulin. The emergence of chronic complications generated a debate about the possible causes of their origin: the metabolic disorder or its consequences [8].

Almost one century afterwards, countless advances in the understanding of normal glucose metabolism, the pathogenesis of diabetes, and the discovery of many effective therapies to treat hyperglycemia and its complications have occurred [3, 6]. Controlled clinical trials have shown the benefits of glycemic control and traditional cardiovascular risk factors (blood pressure, lipoproteins) in reducing the risk of macrovascular and microvascular complications in type 1 and type 2 diabetes [9–12] and confirmed that the targets recommended in 1923 were identical to the conclusions of the Diabetes Control and Complications Trial 70 years later [8]. After one century of scientific advances, large discrepancies prevail between randomized clinical trial findings and implementation "in the real world" [13]. At the same time, the magnitude of diabetes as a worldwide health problem has reached epidemic levels. The "diabesity" (obesity and type 2 diabetes) epidemic is likely to become the largest epidemic in human history [14]. The burden of suffering and death is unprecedented; many nations are unable to satisfy the increasing demand for services [15]. The impact achieved by scientific discoveries reaches a minority of people with diabetes due to a variety of factors.

The Ascent of Diabetes Mortality and Associated Factors. The first measure of the burden of diabetes was of mortality, through the gathering of death certificates in

Europe and America in 1850 when diabetes was still "a rare disease" [16]. For example, in 1866, the death rate from diabetes in New York City was 1.4 per 100,000 residents, and Charles B. Brigham found only 40 death reports from diabetes between 1854 and 1866 (Hurley). Diabetes started to ascend as a relevant cause of death worldwide until the twentieth century. In the United States, diabetes was the 27th cause of death in 1900, and 45 years later, it had become the eighth cause despite the fact that insulin was prolonging life for hundreds of thousands of patients [17, 18]. The average duration in years of life of persons with diabetes in successive eras of treatment, before and after the discovery of insulin, remarkably increased, advancing from 4.9 years in 1897–1914 to 14.4 years in 1944–1949; the age of death had risen from 44 to 64 years, and life expectancy for each group of all cases was approximately 75% that of the general population of similar age [19, 20]. Albeit "it seemed as if the diabetes problem had been solved," an upward continuing trend was documented, except for a drop in 1918–1919 attributed to the influenza pandemic and the sharp fall in death rates after the discovery of insulin from 1922 to 1924 [21, 22]. In developed countries, the incidence of deaths due to diabetic coma has steadily decreased from 86% in the pre-insulin era to 9.6% since 1944, while the frequency of cardiovascular and renal disease has steadily increased [20]. Deaths from infection also declined due to antibiotic therapy, but longer life expectancy increased the risk of cancer mortality [23, 24]. Long-term complications affecting the vascular and nervous systems were present before insulin was available, but their impact was unappreciated because of the short life expectancy after the onset of diabetes [21]. The average age at death of patients with cardiovascular and renal complications was 64 years, which was diagnosed late in life [21].

International standardization and the creation of the mortality data system by the World Health Organization raised awareness about the importance of diabetes as a cause of death and documented differences in mortality rates in different countries and regions [16]. In 1943, the last year in which statistics for the United States were available before World War II, the number of recorded deaths due to diabetes was 36,314, or 35,000 on average per year [24]. One of the best sources of information about diabetes mortality was assembled by E.P. Joslin and his colleagues through collaborations with the Metropolitan Insurance Company and the Massachusetts Department of Public Health [16]. In several reports, they showed increases in the age of death associated with improvements in survival, refinements in the registration of causes of death, and rates of cardiovascular disease and glomerulosclerosis [1–22]. Starting in the 1960s, multiple studies about mortality and its causes in persons with diabetes appeared in the United States, Scandinavia, England, Asia, Africa, Japan, and Germany [16, 25, 26]. These studies reported similar findings in terms of factors predisposing to death (early age of onset, albuminuria, microvascular complications, high glucose levels) and rates of cardiovascular disease and renal failure [25, 26]. At the same time, factors related to long survival were identified, including (1) regular contact with a personal physician, (2) periodic blood glucose measurement, (3) glucose monitoring (initially in urine), and (4) patient support: longevity of parents and grandparents [27].

Estimating the mortality due to diabetes continues to be challenging because more than one-third of the countries in the world have no reliable data, and routine statistics underestimate diabetes deaths resulting from cardiovascular disease, renal failure, or infection [28]. Variations in death certification practices could explain differences in diabetes mortality between countries and distort international comparisons in which countries with more accurate coding practices report higher mortality rates [29]. Despite limitations in the availability and quality of information, diabetes mortality continues to advance at alarming rates, particularly in middle-income countries [28]. In Mexico, for example, only 368 deaths attributed to diabetes were reported in 1922, representing one death per 1000 people dying [30]. These numbers continued to increase in the second half of the twentieth century, reaching 105,500 deaths in 2016 with no decrease in sight, even during the COVID-19 pandemic [31]. In the United States, the number of deaths resulting from diabetes increased by 21.4% in 5 years, from 79,535 in 2015 to 101,106 in 2020, and the excess deaths estimated from diabetes during the COVID-19 pandemic were 2.1–6.5% above the annual percentage change, probably as a result of delayed care or health crises [32, 33].

By comparison to people without diabetes, having diabetes increases the risk of mortality, even in developed countries like Germany, where 21% of all deaths are attributable to diabetes and 16% correspond to type 2 diabetes [34, 35]. In the ninth edition of its Diabetes Atlas, the International Diabetes Federation (IDF) estimated that 4.2 million people aged 20–79 years died from diabetes and its complications in 2019, accounting for 11.3% of the global all-cause mortality in this age group [15].

The Burden of Disease: Prevalence and Costs in 1943. The estimated diabetes prevalence was 3.5 per 1000 [16]. Before 1946, all available estimates were based on interviews or testing of selected groups, but the first surveys from the United States showed that diabetes was not uncommon [17]. Rates of glycosuria in men were above 2.0% among recipients of life insurance from New York in 1909, but mass screening started to be carried out after World War II in the United States and Europe [16]. In 1947, Wilkerson and Krall published the results of the first series of mass screening and detection enterprises in Oxford, Massachusetts, the birthplace of E.P. Joslin, a native-born resident of the town who supported and sponsored them [16, 36, 37]. Seventy-five

years ago, the prevalence of diabetes in this region of the United States was 1.65% [16], and surveys from Europe reported similar prevalence rates in the range of 0.5% to 2–4% [38]. Even in those years, higher prevalence rates, above 30%, were reported among aboriginal subpopulations, like the Nauru, the Pima Indians, and other American Indian tribes [39, 40]. Beyond the challenges involved in collecting accurate data, the prevalence of diabetes has literally soared worldwide. The report of the Non-Communicable Disease Risk Factor Collaboration is eloquent: global age-standardized diabetes prevalence increased from 4.3% in 1980 to 9.0% in men and from 5.0 to 7.9% in women [41]. Accordingly, the number of adults with diabetes in the world increased from 108 million in 1980 to 422 million in 2014 [41]. Estimates from the IDF put the number of people with diabetes at 463 million adults aged 20–79 years in 2019, with the projection that almost 20.4 million live births to women were affected by some form of hyperglycemia in pregnancy [15]. In conclusion, diabetes directly affects approximately half a billion people worldwide, probably twice as many relatives, inflicting a non-precedent personal and economic burden estimated at $1.31 trillion USD, or 1.8% of the global gross domestic product in 2015 [42]. The direct costs of illness are important drivers, but indirect costs account for 34.7%, ranging from one-fifth to almost three-fifths of the total economic burden [42]. Large disparities prevail between high-, middle-, and low-income countries with total health expenditures in high-income countries exceeding those in low-income countries [43].

Trends in diabetes prevalence are increasingly heterogeneous: they are lower in Africa (3.9%) and Europe (8.9%) and higher in North America and the Caribbean (13.3%) [15], but the sustained increase in the largest populated countries is of great concern. In China, for example, the prevalence of diabetes ascended from 0.67% in 1980 to 10.9% in 2013, and the prevalence of prediabetes increased from 2.09% in 1994 to 15.5% in 2008 [44, 45]. In the United States, the prevalence and incidence of diabetes increased by 90% in the first decade of the twentieth century and tripled in some states [46]. Between 2002 and 2012, the adjusted annual incidence of type 1 diabetes increased by 1.8% per year, and the incidence of type 2 diabetes increased by 4.8% per year [47]. The prevalence doubled from 3.5% in 1990 to 7.9% in 2008, while the incidence increased from 3.2/1000 persons in 1990 to 8.3/1000 persons in 2008 [48]. Despite reaching a plateau since 2008, national trends among African-American and Hispanic subpopulations continue to increase [48, 49]. Data from the National Health Interview Survey based on self-report estimated that 0.55% of U.S. adults had been diagnosed with type 1 diabetes, representing 1.3 million adults, and 8.6% had been diagnosed with type 2 diabetes, representing 21 million adults; the weighted percentage of type 1 diabetes was 5.6% and for type 2 diabetes was 91.2% [50, 51]. Interestingly, the percentage of type 1 diabetes was higher among younger adults with a higher education level and a lower body mass index (BMI), while the prevalence of type 2 diabetes was higher among older adults, non-Hispanic Asians, and people with a low education level and a higher BMI [51]. Despite limitations of self-report, validation, and overestimating type 2 diabetes, this study provides information to track the prevalence by type of diabetes, assess the burden of disease, and address the huge challenge of education and prevention programs [50, 51]. In 2019, the estimated number of adults with diabetes in the top ten countries—China, India, and the United States—was 224.4 million, representing 48.4% of the total population with diabetes in the world [15]. In recent years, remarkable discrepancies in the worldwide incidence of diabetes have been observed: since 2006, increasing trends were reported in 33% of populations, 30% had stable incidence, and 36% reported declining incidence [52]. According to the authors of this systematic review, diabetes has continued to rise in developing countries and has plateaued or even declined in developed countries [52]. Contributing factors to these trends represent one of the main challenges faced by diabetes and chronic disease management.

"The New Disease" in Children and Adolescents. To complicate the scenario, the face of pediatric diabetes has undergone striking changes during the last decades, and the incidence of type 1 and type 2 diabetes in children and adolescents is increasing worldwide, along with its consequences, with wide variations in absolute risk (Hurley) [52–55]. At the start of the twentieth century, type 1 diabetes was rare and rapidly fatal; children affected were thin and usually of white race ethnicity, and type 2 diabetes was not considered a pediatric disease [52]. For example, in the United States, the incidence of type 1 diabetes increased at a rate of 1.4% annually, from 19.5 cases/100,000 youths per year in 2002–2003 to 21.7 cases/100,000 youths per year in 2011–2012, but the incidence of type 2 diabetes more than doubled in the same period at 7.1% per year [53]. Over the last decade of the twentieth century, several reports confirmed the association of type 2 diabetes in youth with obesity, especially in minorities; the face of pediatric diabetes has changed [52].

Over two decades, the incidence of type 2 in persons younger than 20 ascended from 9.0/100,000 in 2002–2003 to 12.5/100,000 in 2011–2012 [54]. Having diabetes in youth elevates the risk of complications at earlier ages: Amutha and colleagues in India showed that the frequency of hypertension and hypercholesterolemia and the incidence of retinopathy, nephropathy, neuropathy, and ischemic heart disease are 2.1 times higher in patients with type 2 diabetes [55]. The results of this study are concerning and suggest that 60% of the participants would develop one or more complications of diabetes in one decade and therefore may lose 15 years of

remaining life expectancy [55]. Younger age at diabetes diagnosis is associated with a higher risk of mortality and vascular disease [56]. Young people with type 2 diabetes have a more aggressive form of the disease, including a worse response to glucose-lowering medications, greater insulin resistance, and a higher risk of complications [57]. Venkat-Narayan accurately claims that some countries are winning battles against diabetes [58], while others are losing the war, and some are unable or unwilling to do anything about it [59].

The "Wrong" Lifestyle. The drivers of the diabetes epidemic have been described for decades and involve genetic and environmental risk factors which induce inflammation, autoimmunity, and metabolic stress [60]. Beyond the genetic background of every type of diabetes, the prevalence of type 1 and type 2 diabetes is increasing globally at rates that surpass genetic variation and reveal the key role of environmental factors in both types of diabetes [61]. The pioneering work of David J.P. Barker challenged the idea that chronic diseases like diabetes are explained by bad genes and unhealthy adult lifestyles and proposed that their roots lie in the early life environment [62–64]. Using old birth records, he showed that people of lower birth and infant weight had higher rates of cardiovascular disease, impaired glucose tolerance, beta-cell dysfunction, and diabetes in middle age and proposed a thrifty genotype hypothesis, in which type 2 diabetes is the outcome of the fetus and early infant having to be nutritionally thrifty as a result of impaired growth of beta cells [63, 64]. His statement was visionary: "As long as the individual persists in the undernourished state, there is no need to produce much insulin. However, a sudden move to good or overnutrition exposes the reduced state of beta-cell function and results in diabetes [64]". Further reports have refined Hales and Barker's hypothesis and demonstrated the role of environmental factors in the etiology of obesity, type 1 and type 2 diabetes, and current strong data supporting a genetic-epigenetic predisposition in type 2 diabetes [65–68].

A New Disease in a Changing Environment. Despite remarkable reports showing stabilization and even decline in some countries [69, 70], worldwide trends in overweight and obesity in children [71], adolescents, and adults continue to rise [72, 73]. From 1975 to 2016, the global age-standardized prevalence of obesity increased from 0.7 to 5.6% in 2016 in girls and from 0.9 to 7.8% in boys [71]. From 1975 to 2014, the age-standardized prevalence of obesity increased from 3.2% in 1975 to 10.8% in men and from 6.4 to 14.9% in women, and the prevalence of morbid obesity continues to ascend [72]. Rising trends in children's and adolescents' body mass index have stabilized in many high-income countries, especially at high socioeconomic levels, but have accelerated in east, south, and southeast Asia [71]. Contrary to the dominant paradigm, more than 55% of the global rise in mean body mass index from 1985 to 2017 and more than 80% in some low- and middle-income regions has been due to increases in BMI. If post-2000 trends continue, the bad news is that moderate and severe infant underweight will be surpassed by obesity in 2022, and the analysis of nationally representative data from the United States clearly shows an alarming picture of an obesity epidemic in the future with its related challenges [72–75].

The New Faces of an Old Disease. As a result of changing trends in the epidemiology and phenotype of diabetes over the last two decades, traditional clinical paradigms for type 1 and type 2 diabetes, described as early as 500–600 BC by Indian physicians Sushruta and Charaka and adopted in the first classifications of the 1970s, are being challenged in every age group [76, 77]. Today, diabetes is recognized as a complex and heterogeneous disease that can affect people at different life stages, and the classic phenotypes that were useful to define the types of diabetes are far less useful clinical indicators [76]. In addition to their role in the pathogenesis of type 2 diabetes, obesity, and insulin resistance have become remarkable determinants of type 1 diabetes microvascular, macrovascular, and foot complications [78, 79]. Increasing childhood growth and weight gain augments peripheral insulin demand, which could place greater stress on beta cells and make them more vulnerable to autoimmune attack; reduction in type 1 diabetes is a potential additional benefit of preventing childhood obesity [78, 79]. Metabolic syndrome is particularly useful for cardiovascular risk stratification in younger people, with progressively less impact with increasing age, and while type 1 diabetes is caused by autoimmune destruction of the beta cells, its association with insulin resistance was described as early as 1986 [80]. The unprecedented influence of obesity on the phenotype of type 1 diabetes has resulted in double diabetes, "a new clinical entity" in which clinical features of metabolic syndrome overlap in children and adolescents with type 1 diabetes [76, 81].

On the opposite side of the spectrum, the longtime recognized heterogeneity of type 2 diabetes and its classification has been critically reassessed [82–87]. Metabolic differences suggesting heterogeneous pathways among ethnicities with high risk for diabetes and widely different distributions of BMI support the existence of different molecular mechanisms leading to diabetes presentation and the need to break down patients traditionally classified with type 2 diabetes into new "clusters" or subgroups in order to translate the new subclassification of type 2 diabetes into the clinic with the objective that in a not too distant future, our genetic code will be part of patient records to support clinical decisions and precision medicine [83, 88].

The Bottom Line: Syndemics and Diabetes. Far fewer people globally are underweight than are becoming obese. As economic inequalities have increased worldwide, so have

inequalities in weight and an interplay between genes and the environment [89, 90]. Beyond violence and substance abuse, social inequalities create syndemics: aggregations of two or more diseases or health conditions in populations with some level of the deleterious biological or behavioral interface that exacerbates the negative health effects of any or all of the diseases involved [91]. The syndemics framework was described by Merrill Singer in the mid-1990s and refers to the adverse interactions of all types of diseases (infectious, chronic noncommunicable, mental health, behavioral, from toxic exposure and malnutrition) which emerge under conditions of health inequality caused by poverty, stigmatization, stress, or structural violence [92]. Three elements interact to produce syndemics: disease concentration (genetic predisposition), disease interaction (obesity and insulin resistance, for example), and the large-scale social forces that give rise to them [92]. Syndemics provide an innovative and important alternative to interpret the co-occurrence of noncommunicable diseases like obesity and diabetes, addressing the importance of social conditions in the emergence and medical outcomes [93]. The concept of syndemics departs from traditional medical approaches that treat diseases as distinct entities, detached from the social context of the people suffering from them [94]. It moves beyond the common medical conceptualization of comorbidity and concerns the consequences of disease interaction and the social, environmental, or economic factors that cluster with the diseases and shape their interaction [92]. The role of syndemics in persons with diabetes was brilliantly described by Emily Mendenhall in 2012 in a study about the social context of clustering of diabetes and depression among Mexican immigrant women in Chicago, in which she demonstrated the parallelism between syndemics and the embodiment construct, which states that "we literally incorporate, biologically, the material and social world in which we live (Mendenhall, Krieger)."

The Social Determinants of Health and Diabetes. Beyond the undeniable role of genetic traits in the pathogenesis of diabetes, environmental and social determinants have become preeminent in their ascent and the response at every level, including people with diabetes, providers, and society. In a highly cited study, Christakis and colleagues analyzed the possible contribution of the person-to-person spread of obesity in a densely connected social network of 12,067 people assessed as part of the Framingham Heart Study from 1971 to 2003 [93]. The results showed that clusters of obese persons were present in the network all the time, albeit not solely attributable to the formation of social ties [93]. Among the obese, a person's chances of becoming obese increased by 57% if he or she had a friend who became obese, and if one friend became obese during a given time interval, the other friend's chances of following suit increased by 171% [93]. By comparison, if one sibling became obese, the chance that the other would become obese was 40%, 20% lower [93]. This study highlights the fact that social networks are even more important than genes in determining a person's risk of becoming obese and became a milestone in the story of network medicine [95]. The revolutionary work of Albert Barabasi has shown the existence of networks pervading all aspects of human health [95]. Network-based systems may account not only for the genetic but also for the environmental and social influences of disease [95]. The increasing rates of obesity and diabetes have led the WHO and the scientific community to describe them as epidemics [14, 96]. Traditionally and until today, diseases like obesity and diabetes have been described as "noncommunicable," but current evidence indicates that this formulation is inaccurate [97]. As the study of social networks has demonstrated, behavioral risk factors are acquired through social mechanisms and are thus communicable [97]. A report from the Israeli IDDM Registry Study Group showed that between 1997 and 2014, familial cases of type 1 diabetes increased by 1.9% per year, while sporadic cases decreased by 0.2% per year in the same period [98]. The authors state that the rapid rise in the proportion of familial cases of type 1 diabetes suggests that environmental factors impose higher diabetogenic pressures on patients with susceptible genetic backgrounds [98].

The Social Environment of Diabetes. The inverse care law states that the availability of good medical care tends to vary inversely with the needs of the population served [99]. Social and geographical inequalities in morbidity and mortality persist worldwide, with direct effects on the lifestyle and outcomes of persons with diabetes. The hardships of people with diabetes in achieving effective, multidisciplinary care have been repeatedly documented, even in developed countries, in every age group. For example: (1) children with diabetes in Canada have worse levels of glycemic control if they live in areas of the highest neighborhood index, defined by indicators evaluating economic, social, environmental, and lifestyle factors [100]; (2) lower socioeconomic status and medical insurance are strong predictors of diabetic ketoacidosis readmissions in adults with diabetes in the United States [101]; also in the United States, albeit mortality rates from diabetes decreased from 23.5 person-years in 1997–2001 to 18.1/1000 person-years in 2007–2011, socioeconomic disparities were associated with greater mortality rates in each time period [102].

Food insecurity, defined as the limited or uncertain availability of nutritionally adequate and safe foods owing to cost or distance, is associated with increased consumption of inexpensive food alternatives, which are frequently calorically dense and nutritionally deficient, and increases the risk of obesity and diabetes [103–105]. Compared to people living in food-secure households, food insecurity increases the risk of poor glycemic control (A1c >9.0%), hospitalizations, and visits to emergency departments in adults with type 1

and type 2 diabetes and, through the stress associated with it, negatively affects the ability of patients to perform self-care behaviors [106, 107]. Persons with diabetes and food insecurity have worse glycemic control compared to people who are food secure, and it is likely that multiple factors at the community and individual levels negatively influence diabetes control in the setting of food insecurity [108, 109]. Food insecurity affects all stages of diabetes prevention and control, and people with this condition are at a higher risk of having undiagnosed diabetes [110].

The Preeminence of Context and the Social Determinants of Health. Daneman and the realities of clinical practice confirm that the most common cause of death in youth with type 1 diabetes worldwide continues to be a lack of access to insulin [111]. Despite one century since the discovery of insulin, the life expectancy of children with type 1 diabetes continues to be reduced, and scarcity and costs also affect persons with diabetes from every age group [111, 112]. The five fundamental requirements for diabetes care (availability of food and clear water, availability of insulin and glucose or urine testing, prevention of hyper- or hypoglycemia, and protection against harm) [111] are still—and increasingly—unavailable to a large number of people with diabetes from every age group [112, 113]. Availability and affordability of insulin remain a challenge in many parts of the world [113], and beyond the evidence about their effectiveness, the costs of new therapeutic classes like GLP-1 analogues and SGLT-2 inhibitors are prohibitive for many patients, even in developed countries. Lower socioeconomic profiles are associated with poor glycemic control among children and young adults with type 1 diabetes and with the outcomes, including increased diabetes-related hospitalizations, emergency department attendances, missed outpatient appointments, and a higher risk of complications in patients with type 2 diabetes, but are not part of routine diabetes or clinical assessment [114–118]. Lower socioeconomic position continues to be a risk factor for diabetes and its complications all over the world [114, 118]. Due to the importance of understanding and mitigating the impact of the social determinants of health (SDOH) on the creation of "intractable patterns of higher risk of diabetes, diabetes complications, and mortality" and the role of social inequalities on the vulnerability of people during the COVID-19 pandemic, several professional organizations have published statements on SDOH and calls to action to ameliorate these determinants at the individual, organizational, and policy levels [119, 120].

The Disease, the Illness, and the Predicament. Diabetes is perceived and approached from multiple perspectives including those of patients, their families, physicians, and health professionals. The most important, nevertheless, is from people with diabetes and their families. In 1979, David C. Taylor brilliantly described three different ways of "being sick": (1) diseases, physical entities discernible through diagnostic tests; (2) illnesses, or the experience of being sick; and (3) predicaments, or the complex of psychosocial ramifications, contacts, meanings, and ascriptions which bear on the individual [121]. In our personal and professional experience, we confirm the truth behind these words every day.

The predicament and the positive or negative way in which it is confronted by persons with diabetes and their families are crucially linked to the outcomes. Bob Anderson described it as "the personal meaning of diabetes" and illustrated his statement with five levels of personal responsibility, from absolute denial to total commitment, that every individual has the option to assume [122]. Tinetti and Fried eloquently claimed that:

"Time has come to abandon disease as the focus of medical care. The changed spectrum of health, the complex interplay of biological and nonbiological priorities render medical care centered on the diagnosis and treatment of individual diseases at best out of date and at worst, harmful…clinical decision-making should attainment of individual goals and identification and treatment of all modifiable biological and nonbiological factors, rather than solely on the diagnosis, treatment, or prevention of individual diseases [123]."

A Long Way to Go. Although the conversation has seemingly shifted, paternalism in health care has not changed [124]. Health care systems continue to focus on engaging patients in behaviors that are desirable from a biomedical perspective, with no space left for patient (concerns) goals, needs, desires, abilities, and backgrounds that make humans so rich and diverse [125]. Declining trust in health care has come partly from structural contradictions in health systems in many countries [126]. Health care organizations and providers should consider using language more appropriate for their role in the user's care such as coach, guide, counselor, or advocate, and recognize that despite technological, economic, and political changes, trust in health care fundamentally begins with healing relationships between patients and physicians [125, 126]. Reductionist approaches seek to build holistic constructs for disease etiology, pathophysiology, epidemiology, and therapeutics without including the multiple insertion points of the social world and reduce the "whole person" to pieces that can be coded into data and fed into network analysis [125]. In the twenty-first century, biomedical research and clinical practice have begun to shift from the close examination of disease parts (beta cells, endothelium) toward a "personalized approach" that focuses on the whole person as a unit of analysis [125]. At the same time, medical organizations worldwide have called for a renewed sense of professionalism among physicians based on the overriding principles of patient welfare, patient autonomy, and social justice [127]. These tasks will be complex, time-consuming, and arduous but essential to the advancement of medicine [125, 127].

New Approaches to an "Old" Disease. Diabetes has changed in many ways, each representing a challenge. The "old disease" described in Egypt 35 centuries ago in small numbers of patients has become a worldwide health problem, affecting directly one-sixth of the general population and indirectly at least another sixth of siblings and relatives [128]. The social distribution of the disease leads to large inequalities in management; most of even the "reasonably" expected benefits go to a small fraction of the patients, the ones who have access and can afford it [129–131]. A huge mismatch exists between countries and regions with the largest diabetes burdens and sites of research and clinical excellence [58, 130, 131]. Individuals with suboptimal versus optimal control differ significantly in terms of health care coverage, comorbidities, diabetes-related complications, health care utilization, and cardiovascular risk factors [132]. Even people with economic resources have to endure individualistic, vertical physician approaches and low-quality services. Improvements in the quality of diabetes care [129] and reductions in complication rates among people with type 2 diabetes in the United States and high-income countries [133] are exemplary and contrast with the inability of countries like Mexico, where despite high levels of obesity and diabetes, glycemic control continues to be poor, diabetes is associated with a far worse prognosis than in high-income countries, and complications continue to ascend [134]. Achievements in the science of diabetes are unprecedented, and the future looks even more promising [135–137]. The paradox is unprecedented: never before has there been so much knowledge and resources about diabetes, but never before has there been so much suffering.

The Road Ahead. With the advent of the twenty-first century, science and technology were expected to be formidable forces that would improve population and well-being, but most of the global response to the coronavirus disease 2019 pandemic was unable to realize these hopes. On July 22, 2019, six months before the announcement of the COVID-19 pandemic, a brief communication by Colin Carson and Emily Mendenhall appeared in the Lancet [138]. In their prophetic letter, Carson and Mendenhall warned about three major global challenges: (1) proliferation of closely related emerging viruses, (2) co-occurrence with endemic infections, and (3) interactions with other aspects of health, including noncommunicable diseases (like diabetes), mental health, and stigma, and he made an urgent call to "plan for syndemics of the future [138]." The arguments to establish diabetes as a syndemic are clearly represented and instrumental in advancing the burden of suffering. The COVID-19 pandemic has exposed, once again, longstanding drivers of health inequities, including precarious and adverse working conditions, growing economic disparities, and antidemocratic (and ineffective) political processes and institutions, which exacerbated the vulnerability of societies [139]. From social determinants of health perspective, global economic trends create enduring health hazards for the general population and for people with diabetes, chronic diseases, and comorbidities [139].

A "cascade of care" proposed by Ali and colleagues is a powerful tool to visualize gaps and disparities across groups to improve engagement and the quality of diabetes care, including awareness and the effectiveness of prevention programs for people with prediabetes [140]. Frank Vinicor proposed a Decalogue in which he summarized the challenges facing the future of diabetes [141]. Besides new medicines, it is essential: (1) to continue the improvements in diabetes care, (2) to recognize the complexities of diabetes management, (3) to improve the system of care, (4) to broaden the definition of "medical office" and the delivery of services, (5) to address the dual impact of the diabetes epidemic, through improvements in management and primary prevention, (6) to recognize the role of "non-health forces" influential on diabetes prevention and control, (7) to look for special opportunities for health professionals, (8) to empower patients, (9) to achieve a balance between individuals and communities, (10) to accept and embrace globalization [141]. The challenge is formidable, and the multiple stakeholders involved are required to address the role of the social determinants of health to reduce the persisting and increasing inequalities in diabetes access and quality of care.

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Part I

Magnitude of the Problem from an Individual and Social Context

The Dynamics of Diabetes Prevalence, Morbidity, and Mortality

2

Danilo de Paula, Paula Bracco, and Edward W. Gregg

Introduction

Diabetes mellitus has caught the attention of the world as a major public health problem due to the explosive increases in prevalence that have occurred, affecting virtually all regions of the world and, within regions, affecting all age and demographic subgroups and across the full range of socioeconomic status [1–3]. The estimated global prevalence for 2021 is 536 million, with 10.8% of men and 10.2% of women affected. The highest regional prevalence was registered in the Middle Eastern and North African region (18.1%), while the lowest was in the African region (5.3%). The countries with the highest prevalence were Pakistan (30.8%), French Polynesia (25.2%), and Kuwait (24.9%) [1]. This growth has included both type 1 and type 2 diabetes, although between 90 and 95% of the cases and the predominant increase in prevalence have been driven by type 2 cases [4]. Dozens of individual-level genetic and environmental factors have been prospectively associated with type 2 diabetes, but the increases in prevalence in most societies have likely been driven by a smaller set of trends, including the increasing prevalence of overweight and obesity, declining levels of physical activity, poor-quality carbohydrate in our diets, sugary drinks, increased fast food and portion sizes, aging and a longer lifespan, and increasingly diverse socioeconomics [5, 6]. There is also increasing recognition of heterogeneity in diabetes types, even within the classic categories of type 2 and type 1 diabetes, that likely have different patterns of risk factors that may further vary by region and context [7].

The growth of diabetes prevalence has ominous implications for numerous health and economic-related reasons. Ultimately, diabetes places an enormous burden on individuals, families, health systems, and societies because of the treatment required, the acute and chronic complications, the demand for health services, the direct impact on quality of life, and the loss of years of life [8, 9]. Apart from the already established macrovascular and microvascular complications, reductions in cardiovascular and all-cause mortality are leading to a shift in the morbidity profile and causes of death of those living with diabetes [10–12].

While the growth of diabetes is most apparent in prevalence trends, there are numerous dynamics in the epidemic underway, with important implications for the clinical and public health priorities that follow. We have synthesized primary findings from population studies of the burden and trends in prevalence, incidence, morbidity, and mortality, with a particular focus on the status in North America and Latin America.

Current Burden of Prevalence and Incidence

Prevalence

Countries of the Americas tend to be around the median of the worldwide prevalence of adult diabetes, now estimated at 10.5%, with almost one-in-two adults with diabetes being unaware that they have the condition [1]. The highest estimates from the Americas region come from the Caribbean Islands and Belize, where, except for Aruba, prevalence ranges from 8.7% in the British Virgin Islands to 16.1% in Saint Kitts and Nevis, making it one of the higher diabetes prevalence regions in the world. Similarly, the Central America region contains countries with a particularly high prevalence (Guatemala, the Dominican Republic, Nicaragua, and Puerto Rico), ranging between 9.3% and 13.3% [1]. Prevalence estimates for subregions of the Americas from the Global Burden of Disease Study are generally highest in Mexico, the Caribbean, Central Latin America, and high-income North America, and lowest in Southern Latin

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America, Tropical Latin America, and Andean South America. Other estimates within the past ten years suggest that prevalence is similar for Canada (6.7% diagnosed diabetes in 2014 and an additional 3% undiagnosed in 2007-2009) and Brazil (6.6%) but higher for Mexico (8.9% diagnosed in 2012) and Colombia (12.3% diagnosed in 2016-2017) [13–15]. Prevalence is strongly associated with age, ranging from 2% to 7% across subregions among young adults (age 15-49 years), from 8% to 25% in adults aged 50-69, and from 12% to almost 30% in those aged >70 years.

In the USA, 11.2% of adults have diagnosed diabetes, and 3.4% have undiagnosed diabetes, for a total of 14.6% [16]. The national prevalence in the USA conceals considerable geographic variation, ranging from less than 5% in low prevalence areas of the USA to greater than 16% in high prevalence areas, including areas of concentration in the Mississippi Valley and Deep South, the Appalachian Mountain chain, and selected areas of the West and Midwest corresponding to Native American lands [17, 18]. Prevalence is also notably high in areas corresponding to areas of high concentration of Native Americans and, in Canada, in areas with large populations of First Nations residents.

In the USA, diabetes prevalence is similar across genders but increases steeply with age, such that young adults (age 18-44), middle-aged (45-64), and older (≥65 years), have a prevalence of 2.4, 12.2, and 20.7, respectively. Prevalence also has a strong association with race and ethnicity in the USA, as compared to white women, American-Indians, Alaska Natives, and non-Hispanic blacks have a prevalence that is about twice that of whites, while Hispanics and Asians have a prevalence that is about 80% higher than whites [16, 19]. Education level is also a key factor, as adults with less than a high school education have a prevalence rate of 19.6% that is about 67% higher than that of those with a college or higher education (11.6%) [16]. Within Latin America, indigenous populations have historically had a low prevalence but now represent the populations with the greatest magnitude of recent increase, as evident in indigenous populations in Brazil and Chile [20].

Undiagnosed Diabetes

Because early stages of diabetes are usually without symptoms, many individuals have several years with the disease before detection and diagnosis, and thus a large proportion of the population with diabetes is undiagnosed. In the USA, the prevalence of undiagnosed diabetes is about 3.4%, representing 23.3% of the adult population with diabetes [16]. Older adults, Mexican Americans, and persons with lower education are somewhat less likely to be diagnosed. Although it is commonly believed that awareness and detection of diabetes are increasing over time, changes in the proportion of the population with undiagnosed diabetes converting to the diagnosed state have been relatively unchanged over time, with the exception of recent improvements in detection in older adults, non-Hispanic whites, and wealthy individuals and worsening detection in Mexican-Americans [16, 21, 22]. Few other studies in the Americas have reported undiagnosed diabetes. Considerably higher proportions of cases remaining undiagnosed have been documented in many other regions of the world. Although diagnostic definitions and time periods vary across studies, the proportion of undiagnosed diabetes has been reported to range from 20 to 53% in the South and Central American regions [1]. However, national data from Mexico suggests that up to 50% of cases remain undiagnosed, and in Canada, 20%-40%, depending on the glycemic definition [23].

Incidence

Incidence, or the rate of new cases per population, is less directly affected by mortality rates than is prevalence and is thus a more sensitive indicator of the trajectory of the epidemic. The current adult incidence of diagnosed diabetes is about 6 cases per 1000 adults per year. The incidence is higher for men, with incidence rates of around 7 per 1000 adults, while women had an incidence of 6 cases per 1000 adults in 2019. race-ethnic patterns that parallel the estimates for prevalence [19]. Like prevalence, incidence increases steeply with age, from 4 per 1000 in young adults (age 18-44) to 10 per 1000 in middle age (45-64 years), but there is no further age-related increase thereafter, as incidence is 7 per 1000 among persons aged ≥65, reflecting the age-related incidence peak in the early 60s; Incidence estimates from population-based studies only include the detected cases and thus do not reflect true incidence. When undiagnosed cases are included, estimates in the USA approach 1% per year, and can be used as a general benchmark of the risk of a population, as subpopulations with different designations of prediabetes, such as impaired fasting glucose and impaired glucose tolerance, have incidence estimates that range from 1 to 5% per year [24].

Prediabetes

Estimates of prediabetes vary considerably with the definition used, which remains an area of debate because of the high degree of discordance that exists across different glycemic markers, including fasting plasma glucose, post-challenge glucose response, and HbA1c. Using the American Diabetes Association-like prediabetes definition of fasting plasma glucose or elevated HbA1c, 35% of adult Americans have prediabetes, with estimates ranging from 24% among

young adults (age 18-44) to 47% among adults aged ≥ 65 years [22]. It is noteworthy that, while only about 15% of persons with prediabetes are aware of their risk status, this represents a 50% increase from the last estimates of 10%. Since the risk of progression from prediabetes to diabetes with the ADA definition is relatively low, the Center for Medicare and Medicaid Services (CMS) has adopted a definition of FPG > 110 mg/dl or HbA1c > 5.7%.

Trends and Trajectories in the Epidemic

Prevalence and Incidence

The prevalence of diagnosed and total diabetes has been increasing in most regions for as long as population-based estimates have existed [2, 25, 26]. From 1990 to 2019, worldwide prevalence among adults (20 years of age or older) increased from 4.8% to 8.7% in men and from 4.6% to 7.8% in women, corresponding to an increase in total numbers from 143 to 418 million adults [27]. Diabetes prevalence increased in virtually all regions of the world, with the greatest absolute increases in the Middle Eastern and North African region [27]. Although the growth of mega-urban areas in low- and middle-income countries is often regarded as an accelerator of the diabetes epidemic, large increases have also been observed in rural areas [28].

In the United States, national-level prevalence was first recorded in 1960 at less than 1% of the population and grew steadily in the 1960s through the 1980s to about 3.5% in 1980 (Diabetes in America, 1995) [29–31]. However, in the 1990s, prevalence and incidence increased more rapidly, with a dramatic 50% increase in prevalence from 1990 to 2010 and a continued increase until a peak incidence of 9 per 1000 in 2008 [19]. The increase in prevalence continued from 2009 up to 2018, with total and diagnosed cases being responsible for the trend, while undiagnosed cases remained stable. These trends followed large increases in the prevalence of overweight and obesity occurring during the same period. Throughout this period, the increases in prevalence were paralleled by increases in incidence, from around 4 cases per 1000 per year in the 1980s and early 1990s to almost 10 cases per 1000 adults in 2009 [19, 32].

Prevalence increased in both men and women and in all age groups; the greatest relative increases were observed in youth and young adults, while the greatest absolute increases occurred in older adults [33, 34]. However, the greatest increase in total numbers was observed among middle-aged adults, driven by the USA's baby boom generation, born between 1945 and 1965, reaching the ages of peak diabetes incidence. The increases in diagnosed diabetes increased in virtually all other demographic subgroups of the population, but were particularly notable in those of low education and socioeconomic status, leading to a particular widening of prevalence by social class [32, 35]. This is also evident in geographic trends, where the poorest areas of the USA saw the greatest increase in diabetes prevalence [36].

Impact on Lifetime Risk and Years of Life

The enormous increases in incidence, combined with large decreases in mortality, described in more detail below, have had a large impact on the lifetime risk of diabetes, or the probability of developing diabetes before death, and the number of years spent with and lost due to the disease. Considering Latin America, those metrics have so far have been estimated only for Mexico and Brazil. In Mexico, the lifetime risk through life for women was estimated at 57.7%, whereas for men it was 48.8% [15]. In Brazil, the lifetime risk of diabetes for a healthy 35-year-old woman was 23.8% for those who self-reported as white and 32.2% for those who self-reported as brown or black, the same pattern was observed among men, with a 23.0% and 29.3% risk, respectively. On average, a Brazilian woman diagnosed with diabetes at the age of 35 will lose 2 years of life, whereas a man will lose 4 years [37]. Although this changing burden is a function of both increasing incidence and declining mortality in the diabetic population, the increases and sustained incidence are the predominant factor, underscoring the continued need for effective prevention strategies at the policy, community, clinical, and individual levels.

A Turn of the Tide?

Following the large increases in prevalence in the 1990s, 2000s, and 2010s, data from the U.S. National Health Interview Survey described a peak at an incidence level of 8.5 per 1000 in 2008, followed by a 28% decline to 6.1 per 1000 in 2019 [19]. In contrast with incidence, the prevalence of total and diagnosed diabetes increased from 2009 up until 2018. The prevalence of undiagnosed cases had no significant changes during the period. Similar trends have been reported in state-level prevalence from a separate survey (the Behavior Risk Factor Surveillance System), confirming the encouraging reduction in incidence observed in the NHIS. The reductions appear to have generally affected all major subgroups of the population [33]. Youth and young adults stand out as remaining areas of concern, however, as prevalence and incidence continue to grow in these subgroups [38, 39]. Findings from the SEARCH Study (SEARCH for Diabetes in Youth) revealed a 4.8% yearly increase in the incidence of type 2 diabetes from 2003 to 2012. The increases in incidence were greatest for American Indians and Alaska Natives (8.9% increase), Asian or Pacific

Islanders (8.5%), non-Hispanic Blacks (6.3%), and Hispanics (3.1%), as whites were the only group with no change. Follow-up studies covering the period up to 2015-2017 showed the same annual percent change of 4.8% for both incidence and prevalence of type 2 diabetes, but a change in the most affected subpopulations was observed. In this time period, yearly increases in incidence were greatest for Asians and Pacific Islanders (7.7% per year), Hispanics (6.5% per year), Blacks (6.0%), and American Indians and Alaska Natives (3.7%), and Blacks (3.7). Whites were still the only group with no increase [39–41]. The increases in type 2 diabetes incidence were also accompanied by increases in type 1 diabetes incidence of about 2% per year from 2002 to 2015, and 1.4% from 2009 to 2017, paralleling concerning trends observed in other areas of the world [39, 40].

The continued increases in prevalence and incidence in youth are a discouraging harbinger for the future, given the implications of such early diabetes diagnosis on long-term cumulative diabetes-related complications.

Several explanations for the reduction in incidence have been raised, ranging from true reductions in the rate of the disease due to declining underlying risk in the population, to measurement biases stemming from changes in detection, diagnosis, or definitions of diabetes [32]. Midway through the past decade, surveillance reports also described peaks and decreases in total dietary intake, sugared beverage intake, and plateaus in the prevalence of obesity and physical inactivity. The 2010 American Diabetes Association recommendation to use HbA1c for the diagnosis of diabetes is another potential factor because the HbA1c threshold of 6.5% selects fewer people than the fasting glucose threshold of 126 mg/dl. Thus, a shift from FPG to HbA1c for diagnostic purposes would lower incidence and prevalence [42]. However, if health care providers use both tests, it could actually increase prevalence and incidence. As no surveillance systems measure the actual rates of diagnostic testing or the method of diagnosis, it is unclear how testing or changing awareness of diabetes is affecting incidence rates.

The Burden and Trends in Diabetes Complications

Prevalence and Incidence

Diabetes is notorious for its systemic effect on a diverse array of diabetes-related complications, including macrovascular, microvascular, neuropathic conditions, and infections with coronary heart disease, stroke, foot ulcers, vision loss, kidney failure, amputations, and death regarded as many of the most feared outcomes [43–45]. Diabetes is also increasingly associated with nontraditional complications, including cancers, liver disease, dementia, disability, and other geriatric syndromes [43, 46]. The etiology of diabetes is believed to be multifactorial, with genetic and environmental influences and a key influence of level of glycemic and blood pressure control on most complications.

Diabetic retinopathy is recognized as the signature complication of diabetes and, being the complication that is most specific to diabetes, has been used to guide diagnostic thresholds for diabetes. The prevalence of any diabetic retinopathy has been estimated at 28.5% of the adult diabetic population in the USA, with 4.4% of them having vision-threatening retinopathy [47]. However, no nationally representative estimates of retinopathy exist within the past decade. While it is conceivable that the reductions in incidence of diabetes complications (described in detail below) have served to reduce the prevalence of retinopathy, it is also possible that the concomitant reductions in mortality have resulted in the maintenance of similar or even higher levels of retinopathy.

Chronic kidney disease and coronary heart disease are prevalent at similarly concerning levels in the adult diabetic population, with 19% of adults having stage 3 or stage 4 chronic kidney disease and 18.3% of adults having coronary heart disease [48]. CKD is notably higher in African Americans than in whites, and although coronary heart disease prevalence is similar across race and ethnic groups, a strong gradient with education level has been noted for coronary heart disease, wherein persons with less than a high school education have a prevalence that is 8% points higher (26%) than those with more than a high school education (18%). Although recent estimates of CKD represent a reduction relative to the early 2000s, when prevalence was around one-fourth, there has been no significant reduction in prevalence between 2003-2004 and 2011-2012. Finally, estimates of the prevalence of specific complications do not reveal the full burden of diabetes-related morbidity; when the prevalence of the full range of vascular, musculoskeletal, neurologic, and cancer conditions is considered, most persons with diabetes have multiple chronic conditions present, and the mean number of comorbid conditions is already 3 at the time of diagnosis [49].

Trends in Complications

Despite the high prevalence of morbidity among patients with diagnosed diabetes, there have been large reductions in the incidence rates of diabetes complications over recent decades [29]. In a report of nationally representative data from 1990 to 2010 in the USA, there were substantial declines in a diverse spectrum of diabetes complications, including myocardial infarction, stroke, lower extremity amputation, end-stage renal disease, and hyperglycemic death, resulting in an overall halving of rates of complications for the average U.S. adult with diagnosed diabetes

[29]. The magnitude of decline was greatest for myocardial infarction, declining 68% to draw even with stroke, which also declined by 53%. Rates of amputation declined by 51%, end-stage renal disease by 28%. Rates of death due to hyperglycemia, which were less common in absolute terms, also declined substantially. These reductions in complications generally included men and women and both whites and non-whites. However, the declines in complications were substantially greater in older adults (age > 65 years), moderate in middle-aged adults, and either modest or non-existent in young adults. Although no national data exist on rates of diabetic retinopathy, the prevalence of vision impairment in the USA declined by 25%, from 24 to 18%, paralleling the other improvements in rates. From 2017 to 2019, following a redesign of the survey, the prevalence of visual impairment for all age groups was estimated at 26% [19]. Improvements in diabetes-related complications of a similar magnitude have also been observed for hospitalizations due to vascular disease, amputations, and diabetes in the UK [10].

While the long-term perspective on trends in diabetes complications has clearly been encouraging, more recent reporting of results from the 2010 to 2016 period from the U.S. National Diabetes Surveillance System suggests that the improvements in complications have stalled, and in young adults, even increased [50]. Rates of lower extremity amputations increased overall, particularly among men and the middle-aged population, and were potentially driven by an increase in amputations of the toe, as trends in amputations above the foot have been stable. Similarly, trends in myocardial infarction, stroke, and end-stage kidney disease appear to have plateaued [19, 50–52]. It remains unclear whether such apparent shifting trends are related to changing characteristics of the population with diagnosed diabetes, changes in self-care, risk factor management or treatment, health policy effects, or even broader secular trends in the health of the population.

The encouraging trends in incidence of diabetes-related complications described above take the perspective of the average risk for a person with diagnosed diabetes. When trends in diabetes-related events are expressed as the absolute number of events, wherein the increases in diabetes prevalence over time are permitted to influence rates, the trends have been less encouraging [29]. From this general population burden perspective, rates of diabetes-related MI and mortality declined by 32% and hyperglycemic death declined by 42%, perhaps reflecting the impressive gains that have been made in smoking and the management of hypertension and hyperlipidemia in recent decades. However, trends in amputation stroke have been flat and ESRD has increased when viewed from this population perspective, reflecting the continued wave of new diabetes cases and perhaps an indication that there has been less success in reducing microvascular disease risk than macrovascular disease risk in many countries.

Despite the large reductions in the incidence of diabetes complications, the excess rates of complications associated with diabetes remain substantial, and areas of important disparities remain. Relative risks for lower extremity amputation and ESRD were 10.5 and 6.1, respectively, and adults with diabetes still have an 80% increased risk of myocardial infarction and a 60% increased risk of stroke, respectively [29]. Considerable disparities still exist across subgroups, as non-Hispanic blacks still have more than three times the risk of ESRD, a 50% higher incidence of amputations and stroke, Hispanics have a double incidence of ESRD, and Asians have a 30% higher risk of ESRD than Whites [19]. In addition, compared to women, men have 50% higher rates of ischemic heart disease and more than twice the rate of lower extremity amputation.

Limited population-based data on trends in other areas of the world exists to confirm whether the encouraging trends from the USA are also occurring elsewhere. Although reviews of international data have revealed reductions in rates of lower extremity amputations in numerous settings, these data generally come from Canada, Europe, and Australia. There is limited data on the trends in complications in the Americas or the remainder of middle- or lower-income countries around the world.

Diabetes and Mortality

Adults with diabetes in the USA, Canada, and several countries in Europe have been shown to have overall mortality rates that are approximately 60-80% higher than those of equivalent-aged adults without diabetes [11, 53]. However, data from a Mexico City cohort finding a considerably higher relative risk of death, ranging from 1.9 in persons aged 75-84, to 3.1 in those aged 60-74, to 5.4 for adults aged 35-59 years, serves as a reminder that there may be considerable variation across populations in excess mortality associated with diabetes [54].

Cardiovascular disease is the leading cause of death among adults with diabetes in the United States, accounting for 34% of the total, followed by cancer (20%), diabetes itself, and renal disease. In addition to the five most common causes of death described above, diabetes is associated with an increased risk of several other causes, including unintentional injuries, lower respiratory diseases, sepsis, influenza, and liver diseases. Comprehensive data from the Emerging Risk Factors Collaboration reveals several other specific causes of death that are notably increased in adults with diabetes, including cancers of the liver, pancreas, ovary, and colorectum [53]. These differential rates likely reflect multiple factors, including the chronic hyperglycemia associated

with diabetes as well as the underlying risk factors, including hypertension, insulin resistance, and inflammation commonly recognized in persons with diabetes.

The association of diabetes with mortality varies considerably by demographic subgroup. For example, the relative risk of all-cause, CVD, and renal disease mortality decreases steeply with age. In the USA, among young adults (age 20-44) and middle-aged adults (age 45–64), diabetes is associated with about three times the death rate of those without diabetes. Among those age 65-74, diabetes is associated with twice the death rate and about a 25% increased rate among adults age >75 years. The lower relative risk among older age groups likely reflects several factors, including the possibility that type 2 diabetes onset in young adulthood is a more severe form that is more difficult to manage for physiological as well as environmental and behavioral reasons.

A Diversification of Long-Term Diabetes Associated with Diabetes

Several dynamics in the diabetes epidemic may be leading to relative shifts and diversification in the character of diabetes-related complications [29]. First, the proportionately greater declines in diabetes complications among older adults mean that proportionately more diabetes-related complications now occur in middle age than in previous decades. This is particularly evident in the United States, where adults age 45-64 accounted for only one third of amputations in 1990 and now account for more than half. Second, this may be further compounded by the greater relative increase in diabetes incidence in youth and the earlier exposure to long-term hyperglycemia and the development of diabetes-related complications [55, 56]. The large reductions in cardiovascular disease events and related mortality may be responsible for the relative persistence of end-stage renal disease, as people with diagnosed diabetes are living longer to develop renal disease. Similarly, the reduction in cardiovascular disease mortality observed in most populations with diagnosed diabetes is now accompanied by a proportional increase in deaths due to other causes. Among the US population with diabetes, the proportion of total deaths that were due to cardiovascular causes declined from almost 50% in the early 1990s to 33% in 2010. A similar shift in the specific causes of death has recently been reported in the UK, consistent with the observation of the gradual diversification of the **CVD** types of morbidity associated with diabetes [12]. During the same period, deaths due to cancer in the population with diabetes stayed stable around 18%, and deaths due to all non-CVD, non-cancer causes increased from 33% to 50% of the total. This latter group of "other causes" included several causes, including influenza, pneumonia, sepsis, renal disease, and chronic liver disease, that have an increased association with diabetes. For these latter causes, there has been no improvement or even an increase in the rates in recent decades.

Primary Conclusions and Implications

This synthesis of the epidemiology and trends of diabetes and its complications reveals the following general observations:

1. Changes in the underlying risk of most societies have led to large increases in the incidence and prevalence of diabetes over recent decades, leading to an enormous burden for individuals, families, health systems, and societies.
2. Signs of a peak in the epidemic are apparent in the USA and selected other countries of the world, with recent decreases in incidence and a plateau in prevalence. However, the explanations for these trends are unclear, and the encouraging news is offset by continued increases in diabetes incidence in youth.
3. Diabetes leads to an extensive and diverse array of morbidity, including macrovascular, microvascular, and neuropathic complications and the health outcomes that result.
4. Rates of diabetes-related complications have declined in the USA and other selected countries, likely due to improved risk factor management and organization of care.
5. The disproportionate reduction in cardiovascular disease mortality and increasing lifespan among adults with diabetes, combined with the continued growth of diabetes prevalence in youth, is fueling a diversification of diabetes-related complications and continued population-wide exposure to hyperglycemia that will drive high rates of diabetes-related morbidity into the figure.

ECP: Estimated crude prevalence referes to non-adjusted prevalence of a disease
WNH = white non-Hispanic
BNH = black non-Hispanic
ANH = Aasian non-Hispanic
HIS = Hispanic
LHS = Lless than high school
HS = High sSchool gGraduate
MHS = More than high school
COL = College graduate or above

Multiple-Choice Questions

1. The global prevalence of diabetes is currently estimated to be:
   (a) 278 million
   (b) 324 million

(c) 435 million
(d) **536 million**
(e) 612 million

2. The region with the highest worldwide prevalence of diabetes:
   (a) **Middle East and North Africa**
   (b) Europe
   (c) North America
   (d) Africa
   (e) South Asia
3. Increases in diabetes prevalence are likely driven by:
   (a) By autosomal dominant genetic traits
   (b) By Mendelian inheritance
   (c) **By increasing the prevalence of obesity and overweight**
   (d) By aging and having a longer lifespan
   (e) By socioeconomic factors
4. Current estimated prevalence of adult diabetes in the Americas:
   (a) 5.7%
   (b) 6.8%
   (c) 8.3%
   (d) **10.5%**
   (e) 12.1%
5. The percentage of undiagnosed cases of diabetes among those with diabetes is:
   (a) **23.3%**
   (b) 19.8%
   (c) 16.4%
   (d) 12.5%
   (e) 10.9%
6. Estimated prevalence of persons with prediabetes aware of their risk status:
   (a) 65%
   (b) 50%
   (c) 35%
   (d) 20%
   (e) **15%**
7. Greatest relative increases in diabetes have been observed:
   (a) In newborns
   (b) **In youth and young adults**
   (c) In pregnant females
   (d) In middle-aged adults
   (e) In the elderly
8. The incidence of diabetes in the USA has peaked:
   (a) In the late 1980s
   (b) In the late 1990s
   (c) **In the late 2000s**
   (d) In the late 2010s
   (e) Is still increasing, no observed peak so far
9. Lifetime risk of developing diabetes before death for a 35-year-old woman is:
   (a) 73.2%
   (b) 61.4%
   (c) **57.7%**
   (d) 44.4%
   (e) 38.1%
10. The signature and most specific complication of diabetes:
    (a) Coronary heart disease
    (b) Renal failure
    (c) **Diabetic retinopathy**
    (d) Diabetic foot
    (e) Stroke

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The Economic Costs of Diabetes

3

Joel Rodriguez-Saldana

Paradigms of Medical Care

- "We must do everything, no matter the cost."
- "We must do everything at the lowest possible cost."
- "We must add value to resources."

Introduction

The Value of Health Care. Achieving high value for patients must become the main goal of health care delivery, with value defined as the health outcomes achieved per dollar spent [1, 2]. For a medical condition like diabetes, no single outcome captures the results of care [1]. Outcomes in health care are multidimensional and interactive. Clinicians traditionally are concerned with the clinical outcomes of treatment (Bootman et al. 1996); many of them conceive that economic resources are nonlimited or at least should be and that patients' views and opinions are secondary to their wisdom and expertise. During the last three decades, health care payers and administrators have focused on the economic outcomes of health care decisions, and patients are becoming increasingly knowledgeable and involved in health care (Bootman et al. 1996). They want to know how their quality of life will be affected or about the satisfaction of other patients with the proposed treatment. Clinical, economic, and patient outcomes are closely linked. The true value of health care interventions and programs can only be assessed if all three dimensions of outcomes are measured and considered (Bootman et al. 1996). When aligned and measured, the three outcomes represent health politics [3].

The intrinsic desire to improve patients' perspectives contrasts with the reality of translating the results of evidence-based medicine to all patients and their involved costs. Diabetes costs include the costs of disease at several levels: from individuals to the family, health providers, payers, institutions and society, and the clinical, economic, and patient outcomes obtained by glucose and metabolic control on the natural history of disease. Above all, the patient's vision prevails, as does their longing to receive timely medical care to satisfy their needs for physical and emotional support.

Economics in Health Care: The Basics

Economics is about getting better value from the deployment of scarce resources [4]. Since the 1960s, economists have turned their attention to health services and have considered the economic aspects of different alternatives in the financing, planning, and management of health care [4]. Costs are important in economics, but not more than benefits. Cost is a measure of sacrifice in that since resources are finite, deploying them means a lack of availability for other purposes [4]. Clinicians are usually not aware of the economic resources they consume and the cost of those resources [4]. Health economics is about opportunity cost and benefits because keeping costs down means maximizing the benefits and efficiency of health care [4]. From this perspective, the view that health services (diabetes care in this case) should be about meeting total needs results in confused thinking and romanticism in health care planning [5]. There are not and never will be enough resources to cover all the costs of diabetes care [6]. If this notion of scarcity of resources is accepted, the logic of comparing the costs and benefits of an intervention is more appealing [6]. Resources devoted to an intervention mean less resources available to another. From this perspective, costs should be addressed in terms of benefits sacrificed for the best alternative use of resources: opportunity costs [6]. In some cases, a cost analysis can provide useful information

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but does not consider the relative effectiveness of treatment alternatives, and a cost-benefit approach should be advocated, weighing the benefits and costs of different patterns of care [5]. In other cases, when scarce resources should be devoted to one intervention rather than another, a cost-benefit analysis should be undertaken [6]. One final issue of health economics is ethical: clinical practice requires resources for diagnosis, monitoring, and treatment. The inevitability of considering cost can be perceived for resources over which clinicians have control, but it is not easy when several categories (sources of resources) are not available [7]. Allocation of scarce resources is an everlasting problem despite any utopian dreams of unlimited care for everyone and a variety of efforts and proposals assuming that that dream will become a reality [8]. This issue involves moral questions about justice and equity and implications for quality of life [8, 9]. To summarize, Drummond et al. proposed a series of basic notions of health economics for clinicians wishing to acquire a grasp in the field, including [10]: (1) human wants are unlimited but resources are finite, (2) economics is about benefits, but it is also about costs, (3) health care delivery is only one way of improving the health of the population, (4) choices in health care should always involve value, and (5) reducing inequality always comes with a price [10].

Economic analysis has become an integral component of health programs all over the world. In 2021, the World Health Organization (WHO) reported that global spending on health more than doubled in real terms over the last two decades, reaching 8.5 trillion USD in 2019, or 9.8% of the global gross domestic product [11]. In the same report, the WHO describes the inequalities in the distribution of economic resources: high-income countries account for 80%, of which 70% comes from the government, while low-income countries are highly dependent on out-of-pocket spending (44%), and external aid (29%) [11]. Most concerning is the fact that the share of health in government spending increased in upper-middle and high-income countries, stagnated in lower-middle-income countries, and declined in low-income countries [11]. Out-of-pocket spending is a financial burden for people with diabetes, even in developed countries [12, 13], and is largely unaccounted for in studies about diabetes costs. The high frequency of comorbidities will increase the financial burden of people with diabetes and discourage the continued use of medications that prevent disease progression [14].

To summarize, economic analysis of costs is essential for the following reasons:

1. They are limited and finite, even in developed countries.
2. In countries like the United States, health expenditures have surpassed inflation rates without accompanying reductions in the burden from the leading causes of morbidity and mortality.
3. The competing demands of other programs influencing health (education, employment, nutrition).
4. Persistent deficiencies in the use of economic resources and waste despite scarcity. Increasing resources does not necessarily result in improvements in the quality of health care; it may also reduce it.

Interestingly, developed countries pioneered the design of methods to estimate the costs of disease, measure the results of interventions, and devise strategies to contain the ascending costs of health care.

Economic Analysis and Financial Analysis. Economic analysis consists of the estimate of the net value (the direct and indirect costs) of diseases, whereas financial analysis refers to the comparison of alternative resources, or the "opportunity cost." From the medical and patients' perspectives (when not out-of-pocket), costs would be irrelevant. In the "real world" of limited resources, administrators or payers have to decide. To make these decisions, it is essential to have information about the consequences (outcomes) of different interventions, in terms of not only clinical but also economic effectiveness.

Costs. Medical care involves three types of costs: (1) direct medical costs: directly attributed to the disease and its management, involving screening, prevention, diagnosis, and treatment and including medical visits, medications, and hospital admissions; (2) direct nonmedical costs; (3) indirect morbidity and mortality costs to patients, their families, and society; and (4) intangible costs, short-term and long-term consequences of disease for patients, their families, and society (years of life lost, loss of opportunity for spouses and children [15].

Types of Economic Analysis

Economic evaluation is about costs and consequences (Drummond et al. 2015). It provides a framework to make the best use of clinical evidence through an organized approach to the available alternatives on health, health care costs, and other valuable effects. Economic and clinical evaluations are not alternative approaches; they are essential components to achieving the desired outcomes (Drummond et al. 2015). The evaluation of new or existing health care interventions involves five steps: (1) efficacy: the capacity to achieve its stated goals in optimal circumstances, (2) effectiveness: the demonstration that an intervention does more good than harm, (3) efficiency or cost-effectiveness: the combined assessment of the effectiveness of the health care

intervention and the economic resources required to deliver the intervention, (4) availability: matching the supply of services to the persons who require them, (5) distribution: examination of who gains and who loses by choosing to allocate resources to an intervention instead of another [16].

Efficiency Measures

Three methods are used to assess the economic consequences of interventions: cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), and cost-utility analysis:

Cost-benefit analysis is defined as all of the costs required to achieve a benefit (a clinical outcome) [15, 17]. A main challenge in cost-benefit analysis is the ability to account for all the costs and benefits in monetary units.

Cost-effectiveness analysis is defined as a series of analytical and mathematical procedures that support selecting an intervention [15, 17]. It can be measured in monetary units or clinical outcomes. The main challenge consists of establishing the magnitude of the clinical benefit.

Cost-utility analysis is defined as the total cost to achieve a unit of quantity or quality of life. Measurement units are quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs) [15, 17]. The rationale for using QALYs is that it allows for comparisons of different therapies regardless of health problems or diseases [9].

The Study of the Costs of Diabetes. Every disease involves three types of costs: direct costs, resources used for prevention, screening, diagnosis, and treatment; indirect costs from loss of productivity, absenteeism, early retirement, disability, and early death; and intangible costs from the effect of disease on the quality of life of people. The study of the financial costs of diabetes has covered two complementary fields: (1) cost of illness studies, which initially focused on comparisons of direct costs between people with diabetes and without diabetes and which increasingly include outcomes and (2) comparative analysis of interventions. Costs of illness studies are descriptive, cross-sectional, or longitudinal, relate all costs to a specific disease, and involve two approaches: top-down, or burden of disease, and bottom-up, or person-based. Top-down studies include the direct costs of illness (inpatient, outpatient, nursing home) between people with and without diabetes and have particularly focused on the progressive and lifetime costs of complications and comorbidities. Bottom-up studies involve societal costs and quality-of-life measures. Cross-sectional studies have confirmed the impact of direct diabetes costs on a country's gross domestic product and per capita and the large proportional impact of diabetes on health systems, while incidence-based studies have shown the incremental medical care costs of diabetes before and after diagnosis, showing that the rise in medical spending associated with diabetes begins well in advance of the diagnosis of diabetes, accelerates as diagnosis approaches, immediately after diagnosis, and steeply increases for patients with complications. The study of the financial consequences of diabetes is a recent topic that started with cost-of-illness studies and moved forward to include cost-effectiveness analyses of individual interventions, economic analyses of randomized controlled trials, and systematic reviews. The first studies about the cost of illness were carried out in Sweden, the United Kingdom, and the United States in the 1980s. The initial studies about the cost of diabetes complications started to appear in the 1990s along with evidence about the benefits of metabolic control on the risk of microvascular and macrovascular complications. In the last two decades, the number and scope of studies about diabetes have escalated to include cost-of-disease and cost-effectiveness studies. Table 3.1 depicts a chronological summary of studies about the costs of disease in diabetes, starting with the classical report by Jönsson in Sweden. Beyond depicting the direct and indirect costs of diabetes, over the years, cost of illness studies have been enriched by the inclusion of other relevant variables in the outcomes, like comorbidities, avoidable hospital admissions, and patient outcomes:

The Economic Burden at the Global Level. Measuring the global costs of diabetes confirmed the magnitude of the problem and revealed persistent limitations in objective measurement [66–68]. In 2015, a systematic review by Seuring et al. reported large variations in methods and cost estimates and the absence of control groups in most studies, resulting in large differences in direct and indirect costs. In their review, direct costs ranged from $242 USD on out-of-pocket expenditures in Mexico to $11,917 USD for direct costs in the United States. Indirect costs show similar variations: from $45 USD in Pakistan to $16,914 USD in the Bahamas [66]. Interestingly, and in stark contrast with high-income countries, a substantial part of the cost burden comes out-of-pocket. Regression analysis revealed that direct costs are positively associated with the gross domestic product of each country and that the United States has particularly high costs [66]. In 2017, Bommer et al. published the results of the first global cost-of-illness study building on the methods of the IDF Diabetes Atlas, in which the estimated cost of diabetes in 2015 amounted to $1.31 trillion USD, or 1.8% of the world gross domestic product (GDP) [67]. In their report, indirect costs represented 34.7% of the total, due to labor-force dropout (48.5%), absenteeism (3.9%), presenteeism (2.1%), and death [67]. Morbidity-associated factors dominate in high-income countries, whereas premature mortality

Table 3.1 Studies about the costs of diabetes

Year and country	Author and reference	Type of study	Results
1983 Sweden	Jönsson [18]	Inpatient statistics from 19 county councils in 1977	Total economic costs in 1978: 1300 million SEK
			Institutional care: 2/3; noninstitutional care: 1/3 of direct costs
			Direct costs: 43% of the total
			Indirect costs: 57%, dominated by permanent disability: 60%
			Higher share of direct costs for diabetes than for cancer, cardiovascular or musculoskeletal diseases
			Total number of bed days: 656,000
			Hospital discharges: 25,700
			A slow decrease in admissions for acute care since 1970, an increasing number of bed days in long-term care
			Years lost from retirement: 8000
			Total loss of production caused by early retirement: 438 million SEK
			Direct costs from management: 313 million SEK
			Direct/indirect costs from complications: 1004 million SEK
			Total loss of production caused by premature death: 176 million SEK
1989, UK	Gerard et al. [19]	Cost of illness study, including: (1) direct costs, (2) indirect costs, (3) welfare effects from disability or distress	Total direct costs: £238.9
		Estimation as the sum of inpatient, outpatient and primary care costs	Total indirect costs: £343.0 million
1989, USA	Huse et al. [20]	Estimations based on the prevalence of diabetes, microvascular and macrovascular complications and mortality in people with type 2 diabetes	Total costs in 1986: 19.8 billion USD
			Direct costs: 11.6 billion USD
			Indirect costs including disability and premature death: 19.8 billion USD
1991, France	Triomphe [21]	National estimation extrapolated from a sample of 109 patients with type 1 and type 2 diabetes	Average medical costs: type 1, 12,178 FFr; type 2, 6908 FFr
			Distribution of costs:
			Type 1 Diabetes
			Hospitalizations: 33.9%
			Laboratory tests: 4.9%
			Medical visits: 5.5%
			Medications: 44.7%
			Other: 11.0%
			Type 2 Diabetes
			Hospitalizations: 40.1%
			Laboratory tests: 5.7%
			Medical visits: 8.1%
			Medications: 34.3%
			Other: 11.8%
			Hospital admissions: 144,936; percent of the total: 2.2%
			Hospital costs of diabetes in 1987: 195,500 billion FFr; percent of the total: FFr: 1.7%

1991, USA	Jacobs et al. [22]	Cost of illness study	Hospital admissions in excess of those occurring in the general population in 1987: 786,903; 2.0% of the total
		Data from the National Hospital Discharge Survey to estimate the cost of hospitalizations from chronic complications	Total cost of inpatient care: $5091 million
			Cardiovascular complications: 74%
			Renal disease: 10%
			Neuropathy: 3.6%
			Ophthalmic disease: 1.5%
1992, USA	Rubin et al. [23]	Cost of illness study	Hospital admissions from acute complications: 372,000
		Data from the National Medical Expenditure Survey 1987	Emergency visits: 647,000
			Hospital admissions from chronic complications: 731,000
			Medical visits: 15.700 million
			Visits to dietitians: one million
			Glucose monitors: 9.4 million
			Prescriptions of antidiabetics and insulin: 41 million
			Direct costs: 45.2 billion USD
			Economic expenditures per capita
			People with diabetes: $9493.00 USD
			People without diabetes: 2604.00 USD
			Percentage of expenditures devoted to the management of complications: 50% of the total
			Percentage of the total health expenditure devoted to diabetes: 15%
1996 Finland	Kangas et al. [24]	Cost of Illness study	Total health expenditure per patient:
		30,266 questionnaires receiving medications through pharmacies in Finland in 1989	With diabetes: $3941 USD
			Without diabetes: $1326 USD
			Total costs represent 5.8% of the total health expenditure, were three times higher than the average health costs for people without diabetes, and were distributed as follows:
			Inpatient care: 81%, 13% of all available hospital beds in the country
			Medications: 9%
			By comparison, the cost of ambulatory care and resources for self-care is lower, amounting to 8% and 2%, respectively
1998, Sweden	Henriksson and Jönsson [25]	Cost of illness study	Economic burden of diabetes in Sweden in 1994: 5746 million SEK
			Direct costs: 2455 million SEK, 43% of the total
			Indirect costs: 3291 million SEK
1998, USA	American Diabetes Association [26]	Cost of illness study	Total medical expenditures in the United States in 1997: $77.7 billion USD, $10,071 USD per capita
		National Health Care Survey Data	Direct costs: $44.1 billion
			Acute care costs: $7.7 billion
			Chronic complications: $11.8 billion USD
			Excess prevalence of general medical conditions: $24.6 billion USD
			Proportional costs: Inpatient care: 62%
			Outpatient care: 25%
			Nursing home care: 13%
			Indirect costs: $54.1 billion USD; from premature mortality: $17.0 billion USD, from disability: $37.1 billion USD

(continued)

Table 3.1 (continued)

Year and country	Author and reference	Type of study	Results
1998, USA	O'Brien et al. [27]	Cost of disease study	Direct medical and indirect expenditures attributable to diabetes in 1997: $98 billion USD
		Data from multiple sources to estimate direct medical costs on managing type 2 diabetes chronic complications and hypoglycemia	Hospital costs: 62%
			Ambulatory costs: 25%
			Nursing home care: 13%
			Average event costs:
			Acute myocardial infarction: $27,630 USD
			Cerebrovascular events: $40,616 USD
			End-stage renal disease: $63,659 USD
			Blindness: $3486 USD
			First low extremity amputation: $26,894 USD
			Second low extremity amputation: $27,132 USD
			Hypoglycemia: $188 USD
			Indirect medical costs increased from $46.6 billion in 1992 to $54.0 billion in 1997 due to an increase in the number of people with disabilities from diabetes
			With a prevalence of 3.0%, total expenditures for diabetes comprised 8% of health care expenditures in 1997, a more than fourfold difference compared with people without diabetes
1999, USA	Brown et al. [28]	Analysis of clinical data from 11,768 patients with type 2 diabetes to assess the progressive costs of complications	Per-person costs increased from baseline:
			Variable from primary to specialized care
			By more than 50%, from $1087 USD to $2033 USD over 9 years after initiation of a cardiovascular drug
			By 360% after a major cardiovascular event
			By 65% with abnormal renal function
			By 195% with advanced renal disease
			By 771% with end-stage renal disease
			Greatest cost savings would be achieved by preventing major cardiovascular events and progression to stage 3 renal disease
2000, Sweden	Henriksson et al. [29]	Cross-sectional, cost of disease study	Total annual direct costs in Sweden in 1998: 7 billion SEK, 6% of the total health care expenditures, more than four times higher than a previous national estimate
		Estimate the direct costs of type 2 diabetes and the influence of complications	Annual per patient cost: 25,000 SEK, 42% from hospitalizations
			Hospitalization costs: 2.7 billion SEK
			Hospitalization cost per patient: 10,599 SEK
			Ambulatory costs: 2.161 billion SEK
			Ambulatory costs per patient: 7719 SEK
			Medication costs: 1.8 billion SEK
			Medication costs per patient: 6665 SEK
			Costs in patients with macro and microvascular complications:
			Hospitalization: 29,555 SEK
			Ambulatory care: 11,053
			Medications: 9520 SEK
			Average costs for patients without complications: 24,983 SEK
			Average costs for patients with complications: 50,128 SEK
			Difference: 25,145 SEK
			Higher costs with longer duration of disease, from 20,977 SEK with less than 5 years to 22,059 SEK between 5 and 10 years

2000, USA	Nichols GA et al. [30]	Cost of disease study	An economic burden from impending diabetes is apparent for at least 8 years before diagnosis, beginning with outpatient and pharmacy services ranging from $156 to $245 USD/year
		Review of electronic records of a large health maintenance organization to describe and analyze medical care costs 8 years before the diagnosis of type 2 diabetes	The single class of drugs with the highest incremental costs were antihypertensives
			Incremental costs averaged $1205 USD per type 2 diabetes patient per year, including $1913 USD each year for the 3 years preceding diagnosis
2001, Sweden	Norlund et al. [31]	Cost of disease study	Physical dependence increased from 1.3% in people younger than 65 years to 14.6% in those aged 80 years or older
		1677 people with diabetes from the catchment area of Southern Sweden, 2.4% of the total population	Leading diabetes complications included:
		Interview and physical examination to establish physical dependence and comorbidities	Retinopathy, proliferative: 32.9%
		Health depreciation as a capital asset as a result of illness and death	Foot problems: 31.3%
			Ischemic heart disease: 22.1%
			Congestive heart failure: 14.5%
			Cerebrovascular disease: 11.3%
			Foot ulcers: 8.4%
			Total direct and indirect costs per person with diabetes in SEK: 61,738 Total direct costs: 36,173
			Distribution:
			Home-help hours: 11,315
			Inpatient days: 11,294
			Retirement home: 4795
			Nursing home: 3085
			Nurse visits: 1984
			If no monetary value was assigned to home help by relatives, the total average cost would be reduced by 10%
			Total indirect costs: 25,565
			Distribution:
			Early retirement: 19,610
			Sick days: 5955
			Incremental use of resources in 1 year by people with diabetes was 1.2 more medical visits and 5.3 more nurse visits
			Compared with people without diabetes, the incremental losses in production amounted to 9.4 sick days
			Frequency of early retirement: 14.2% higher
			When diabetes-related complications are included, the cost of disease is 2–3 higher
			The incremental costs are more than double for the population
			Diabetes generates high costs to society

(continued)

Table 3.1 (continued)

Year and country	Author and reference	Type of study	Results
2003, USA	American Diabetes Association [32]	Cost of illness study	Total medical expenditures in the United States in 2002: $132 billion USD
		Based on an estimate of 12.1 million people in the United States in 2002 diagnosed with diabetes, an increase of 1.8 million (1.7%) from year 1997 estimates	Health care expenditures: $92 billion
			$13,243 USD per capita
			Direct costs: $91.8 billion, 52% for people ≥65 years
			Hospital inpatient care: $40,337 billion USD, 31% of the total
			Nursing home care: $13,878 billion USD, 11%
			Outpatient care: $20,130 billion USD, 13%
			Proportional costs: Inpatient care: 31.0%
			Emergency visits: 2%
			Outpatient care: 15.0%
			Nursing home care: 11.0%
			Indirect costs: $39.8 billion USD
			Lost productivity from disability: $7.5 billion USD
			Premature mortality: from diabetes: 21.5 billion USD
			The estimates are conservative and probably underestimate the true costs of diabetes
2004, Mexico	Arredondo and Zúñiga [33]	Cost evaluation method based on instrumentation and consensus techniques	Comparing the economic impact in 2003 vs. 2005, a 26% increase in financial requirements was observed
			Total costs: $317,631.206 USD
			Direct costs: $140,410.816
			Indirect costs: $177,220,390
2010, Mexico	Rodríguez Bolaños et al. [34]	Cost of illness study	Total direct costs: $452,064,988 USD, 3.1% of operating expenses
		Review of medical charts from 497 patients from a social security institution treated at secondary and tertiary medical care units from 2002 to 2004	Annual average cost per patient: $3193.75
			Cost per patient without complications: $740.34
			Cost per patient with complications: $3550.17 USD
			It is essential to identify possible savings, redistribute economic resources, and improve medical care at the early stages of the disease
2011, UK	Simmons and Wenzel [35]	Cross-sectional, retrospective 12-month audit in a single teaching hospital to assess mortality, bed day per year and diabetes attributable hospitalization cost	4864 diabetes hospital admissions, 12.9% of the total
			Bed occupancy: 13.9%
			Risk of death among people with diabetes: 18.1% higher
			Mean bed days:
			Men with diabetes: 10.9 vs. 6.3 in men without diabetes
			Women without diabetes: 11.4 vs. 5.9 in women without diabetes
			Mean costs
			People with diabetes: £5835
			People without diabetes: £3706
			Diabetes attributable hospitalization cost: 46.5%, an HbA1c >10% was associated with excess hospitalization
			Approaches known to reduce hospitalization through the improvement of primary diabetes care are urgently required

2011, USA	Nichols, Vupputuri, Lau [36]	Cost of diabetes study to estimate the direct medical costs of patients with type 2 diabetes and hypertension by the level of proteinuria to evaluate differences between patients with and without nephropathy progression	Patients with normoalbuminuria who progressed to microalbuminuria experienced an annualized change in baseline costs that was $396 USD higher than those who maintained normal albuminuria ($902 vs. $506)
			Among patients with microalbuminuria, progression was significantly associated with a $747 USD difference in annualized change in outpatient costs compared with no progression ($1056 vs. $309)
			Among patients who progressed, costs were 37% higher following progression from normoalbuminuria to microalbuminuria ($10,188 vs. $7424), and 41% higher following progression from microalbuminuria to macroalbuminuria ($12,371 vs. $8753)
			Progression of diabetic nephropathy is strongly associated with higher subsequent medical care costs in hypertensive patients with diabetes
			Preventing progression from normo- to microalbuminuria and micro- to macroalbuminuria may reduce the economic burden of diabetic nephropathy
2013, USA	Zhuo, Zhang, Hoerger [37]	Cost of disease study	Lifetime direct costs of treating type 2 diabetes and complications according to the age of diagnosis in men:
		Type 2 diabetes simulation model to simulate disease progression and direct medical costs among a cohort of newly diagnosed type 2 diabetes patients based on the 2009–2010 National Health and Nutritional Survey	25–44 years: $124,700 USD
			45–54 years: 106,200 USD
			55–64 years: $84,000 USD
			≥65 years: 54,700 USD
			Lifetime direct costs of treating type 2 diabetes and complications according to age of diagnosis in women:
			25–44 years: $130,800 USD
			45–54 years: 110,400 USD
			55–64 years: $85,500 USD
			≥65 years: 56,600 USD
			Effective interventions that prevent or delay type 2 diabetes and diabetic complications might result in substantial long-term savings in health care costs
2014, Spain	Arrieta et al. [38]	Cost of illness study from a descriptive, cross-sectional analysis of a sample of 3268 patients with type 2 diabetes	From an estimated population of 390,944 people with diabetes, 172,406 will experience macrovascular complications and 212,283 will experience microvascular complications during their lifetimes
			The mean cost of complications per patient is estimated at EU 4121.54, 66% from macrovascular complications
			Total costs from diabetes complications: EU1.611 billion, EU1.065 billion from macrovascular complications, 545 million from microvascular complications
			The economic impact of diabetes complications will increase with higher diabetes prevalence

(continued)

Table 3.1 (continued)

Year and country	Author and reference	Type of study	Results
2015, USA	Ozieh et al. [39]	Cost of illness study from 2053 adults with diabetes registered in the 2011 Medical Expenditure Panel Survey	Percentage of patients with self-reported chronic kidney disease (CKD): 9.7%
			By comparison of a $9689.49 USD expenditure in people without CKD, the unadjusted medical expenditures from CKD amounted to $20,726 USD
			Adjusted mean expenditures were $8473 USD higher
			Estimated unadjusted total expenditures for CKD: more than $43 billion USD in 2011
			CKD is a significant contributor to the financial burden for people with diabetes, minorities, and the uninsured experience barriers in accessing care
2016, Iran	Davari et al. [40]	Cost of illness study	Mean total costs
		Retrospective observational study	Public fees:
		Analysis of medical records of 2898 people with Type 2 diabetes from a tertiary care center to estimate 1-month direct costs	Laboratory tests: $20.4 USD
			Medications: $65.9 USD
			Medical visits: $17.9 USD
			Private fees:
			Laboratory tests: $52.4 USD
			Medications: $67.8 USD
			Medical visits: $35.6 USD
			Outpatient direct costs for diabetes increased 14.6 times over 10 years
			Medications are the main component
			Estimated national direct costs of diabetes: $810 million USD
2016, Denmark	Sortso et al. [41]	Cost of disease study	Total health care costs: EUR 1.64 billion
		To investigate the relationship between costs, with and without complications in a National Diabetes Register	Cost per person-year: EUR 5509
			On average, a person with diabetes without complications consumes twice as many health care resources as a person without diabetes
			With complications, a person with diabetes consumes three times the health care resources with higher gradients among younger patients, men than women, and for secondary care
			From no complications to minor or major complications, increased health care costs ranged from EUR 1782 to EUR 7534
			Productivity loss amounted to EUR 1.77 billion
			Patients with diabetes received on average a lower income than people without diabetes
			Additional costs were estimated to be EUR 761 million
			Total costs of diabetes in 2011: EUR 6.67 billion
			Diabetes costs increase with increased complications, providing an economic rationale for secondary prevention
2016, Mexico	Lugo-Palacios, Cairns [42]	To estimate the financial and health burden of diabetic ambulatory care sensitive hospitalizations (ACSHs) from public general hospitals at a national level, 2001–2011	Over one decade, 195,778 ACSHs were identified, accounting for one-fifth of total ACSHs for any cause
			Total ACSHs due to diabetic complications increased >130% over 10 years
			The estimated financial costs due to diabetes complications increased 125%
			Diabetic foot hospitalizations showed an increasing trend, growing by 160% and surpassing renal failure
			Estimated DALYs increased by 112%; renal failure had the highest health burden
			Despite promotion and prevention efforts to improve the control of diabetes across the health system, the financial and health burden of ACSHs associated with diabetes complications increased dramatically
			Given the WHO cost-effectiveness criterion, it would have been cost-effective to spend $1.146 billion USD on primary care interventions to avoid the DALYs associated with diabetes complications

2016, Mexico	Lugo-Palacios, Cairns, Masetto [43]	To estimate the financial and health burden of diabetic ambulatory care sensitive hospitalizations (ACSHs) in a large social security institution 2007–2014	Over 7 years, 322,977 ACSHs were identified, of which kidney failure and diabetic foot represented 78%
			Diabetes complications increased 10.3% over this period
			Multiple admission for the same complications occur in 15% of patients
			Diabetes costs increased by 8.4% in 7 years, with kidney failure as the most important cause, accounting for 43% of costs
			Estimated DALYs decreased by 13.6%, representing more than 50% of the estimated total
			Timely and effective primary care could reduce the burden of preventable hospitalizations
			Resources used to treat avoidable hospitalizations could be used to fund more and better primary care
2017, Israel	Porath, Fund, Maor [44]	Cost of illness study in a large health maintenance organization	Median annual cost in cost units (CU): 4420
		Retrospective analysis, 1 year duration	Differences between costs for people with diabetes and people without diabetes accounted for 85% of people 35–44 years old and 24% of people 75–84 years old
			Medical costs increased similarly for patients with controlled and poorly controlled diabetes and with comorbidities
			Costs were significantly impacted by kidney disease
			Leading factors affecting costs were HbA1c level, male gender, chronic diseases, diabetes complications, disease duration, and stage of renal failure
			Early treatment of diabetes and its complications is cost-effective
2017, Hong Kong	Jiao et al. [45]	Cost of disease study to estimate medical costs associated with diabetes complications from the Hospital Authority Clinical Management System through modelling	Expected baseline cost of a 65-year-old person without complications: $1521 USD
			Stroke and foot ulcers had the highest incremental costs
2017, Germany	Jacobs et al. [46]	Cost of illness study based on a random sample of all German people with statutory health insurance	Per capita costs for people with type 2 diabetes: EUR 4957 in 2009, EUR 5146 in 2010
			People with diabetes had 1.7-fold higher health expenses than people without diabetes, with the largest expenses in medications and inpatient treatment
			Medical care for people with diabetes accounts to 10% for total health insurance expenses
2017, USA	American Diabetes Association [47]	Cost of illness study from national surveys, Medicare standard analytical files and claims databases for the commercially insured population	Total estimated direct costs of diabetes in 2017: $327 billion, including $237 billion in direct medical costs and $90 billion in reduced productivity, accounting for one in four health care dollars
			Average medical expenditures per year: $16,750 USD
			Medical expenditures for people with diabetes are 2.3 times higher than expenditures for people without diabetes
			Indirect costs include increased absenteeism ($3.3 billion USD), reduced productivity at work ($26.3 billion USD), reduced productivity for people outside the labor force ($2.3 billion USD), inability to work because of disease-related disability ($37.5 billion USD), and loss of productivity due to premature death ($19.9 billion USD)
			After adjusting for inflation, the economic costs of diabetes increased 26% from 2012 due to the increased prevalence of diabetes and the increased cost per person with diabetes
2018, USA	Squires et al. [48]	Cost of illness study	Diabetes costs increased from $37 billion USD in 1996 to $101 billion in 2013
		Estimates extracted from a health metrics database from 1996 to 2013	In 2013, the greatest amount of health care spending occurred on medications (57.6%), followed by ambulatory care (23.5%)
		Disease burden was extracted from the Global Burden of Disease 2016 Study	Between 1996 and 2013, pharmaceutical spending increased by 327%, especially by 144% increased pharmaceutical spending between 1996 and 2013

(continued)

Table 3.1 (continued)

Year and country	Author and reference	Type of study	Results
2018, USA	Shresta et al. [49]	Cost of illness study using data from three national 2013–2014 databases to estimate direct costs and a human capital approach to estimate indirect costs	The estimated median state economic costs were $5.9 billion USD, ranging from $694 billion to $55.5 billion in total
			The estimated cost per person with diabetes was $18,248, ranging from $15,418 to $30,915 per person with diabetes
			The estimated direct medical costs ranged from $2.8 billion to $8.5 billion, and indirect costs ranged from $3.0 billion to $9.6 billion
			Indirect costs were larger than costs from mortality
			Economic costs for diabetes vary extensively across U.S. states, and are not associated with the size of the population
2018, Germany	Kähm et al. [50]	Cost of disease to estimate costs associated with diabetes complications using statutory health insurance data from 316,220 patients with type 2 diabetes in 2013–2015	Base case estimated total costs for the example of a 60- to 69-year-old man: diabetic foot EUR1293, amputation EUR14,284, retinopathy EUR671, blindness EUR2933, nephropathy EUR3353, end-stage renal disease EUR22,691, fatal stroke EUR11,176, nonfatal myocardial infarction/cardiac arrest EUR8035 EUR, nonfatal ischemic heart disease EUR6548, fatal ischemic heart disease EUR20,942, chronic heart failure EUR3912, angina pectoris 2965, retinopathy EUR6130
2018, Ireland	O'Neill et al. [51]	Cost of illness study from a nationally representative sample of 8107 adults aged ≥50 years	Incremental cost from diabetes: EUR 88,894,421
			Compared with people without diabetes, diabetes was associated with 1.49 additional visits to general practitioners annually, with an 87% increase in outpatient visits, a 52% increase in hospital admissions, and a 33% increase in accident and emergency department attendances
			Diabetes is associated with substantial health services use and costs; costing of hospital admissions was EUR60,002,421, accounting for more than two-thirds of the cost burden
			Areas for potential cost savings include a shift in routine management to primary care and improved access to effective ancillary services such as foot care and dietetic interventions
			These findings outline the urgent need to invest in the prevention and management of diabetes
2018, France	Charbonnel et al. [52]	Cost of disease study from a random sample of 600,000 patients registered in a national health insurance database	Extrapolating the results to the whole population with type 2 diabetes in France, the total estimated direct costs amounted to EUR8.5 billion in 2013, corresponding to 5% of all health care expenditure. Per patient medical expenditures were EUR6506 for patients with type 2 diabetes as compared with EUR3668 in the control group
		Cost analysis from a sample of 25,987 patients with type 2 diabetes matched with a control group of 76,406 individuals without diabetes	Cost difference between the two groups was EUR2838 per patient per year, mainly due to hospitalizations (33.2% of the total costs), medications (23.7%) and nursing care (10.9%)
			Total per capita annual costs were lowest for patients receiving metformin monotherapy (EUR4153) and highest for those receiving insulin (EUR12890)
			These results highlight the importance of public health programs aimed at reducing the incidence of type 2 diabetes, preventing diabetic complications through better glycemic control, reducing clinical inertia and improving patient adherence, and developing less costly integrated care programs

2018, USA	Lin, Pope, Zhou [53]	Retrospective observational study on 138,466 privately insured adults newly diagnosed with type 2 diabetes who were classified into five comorbidity groups: (1) concordant only, (2) discordant only, (3) both concordant and discordant, (4) any dominant, (5) none, to investigate the influence of type of comorbidity on health care utilization and costs	Comorbidities were significantly associated with higher health care costs and the magnitude of the association varied with comorbidity type
			Type of comorbidities and costs:
			Discordant only conditions: 27%, $9173 USD
			Dominant conditions and costs: 25%, $38,168 USD
			Concordant and discordant conditions: 24%, $20,401 USD
			Concordant conditions only: 7%, $9000 USD
			No comorbidities: 21%, 3365 USD
			53% of the total costs were attributable to 25% of patients with comorbidities
			Dominant comorbidities and concordant plus discordant comorbidities substantially increase diabetes costs
			Diabetes management must explicitly address comorbidities to address distinctly different health needs and utilization patterns
2018, Mexico	Salas-Zapata et al. [54]	Cost of illness study to estimate the direct costs related to hospitalizations for diabetes and its complications in a social security institution from 2008 to 2013	Hospital discharges during the period of study: 411,302
			Direct costs: $1.563 USD billion, 77.26% for type 2 diabetes, 22.74% for type 1 diabetes
			Magnitude of costs according to complications:
			Renal failure and peripheral arterial disease account for 46% of hospital admissions
			Hospital admissions show an increasing trend in men and in the 15–44 age group, with decreasing amounts in people ≥65 years
			Diabetes management should be multidisciplinary; health institutions should devise strategies supporting diabetes prevention and control
			Costs from hospitalizations could be reduced by delivering optimal primary care
			Essential costs to be addressed include indirect and out-of-pocket costs
2019, USA	Shresta et al. [55]	Cost of illness study to examine changes in diabetes-related preventable hospitalization costs and to determine the contribution of each underlying factor to these changes	During 2003–2014, the estimated total cost of diabetes-related preventable hospitalizations increased annually by 92.9 million USD (1.6%)
		Data from the Nationwide Inpatient Sample for adults to estimate trends in costs in US dollars in total and by condition, including short-term complications, uncontrolled diabetes and lower extremity amputations	Of this 1.6% increase, 75% was due to the increase in the number of hospitalizations
			The cost of short-term complications, lower extremity amputations, and long-term complications increased annually by 4.2, 1.9, and 1.5%, respectively, while the cost of uncontrolled diabetes declined annually by 2.6%
			Total costs associated with preventable hospitalizations increased despite substantial improvements in preventable hospitalizations and reduced lengths of stay, which were offset by increasing costs per day and increases in the size of the diabetes population
2019, USA	Dall et al. [56]	Cost of illness study to estimate the economic burden of undiagnosed diabetes, prediabetes, and gestational diabetes (GDM) in 2017, including state-level estimates from three databases of 5.8 million, 2.8 million and 7.1 million records from 2013 to 2015, in addition of data from the U.S. Census Bureau, the Centers for Disease Control and Prevention and Centers for Medicare & Medicaid Services	Direct costs associated with diabetes, undiagnosed diabetes, prediabetes, and gestational diabetes in 2017: $404 USD billion
			Distribution
			Diagnosed diabetes: $327.2 billion
			Undiagnosed diabetes: $31.7 billion
			Prediabetes: $43.4 billion
			Annual burden per case
			Diagnosed diabetes: $13,240 USD
			Gestational diabetes: $5800 USD
			Undiagnosed diabetes: $4250 USD
			Prediabetes: $500 USD
			The economic burden of diabetes for each US citizen in 2017: $1240 USD
			It is urgent to adopt more comprehensive approaches and better prevention and treatment strategies

(continued)

Table 3.1 (continued)

Year and country	Author and reference	Type of study	Results
2020, USA	Crossen et al. [57]	Retrospective analysis of type 1 medical costs 2012–2016 from a comprehensive database of 9445 individuals aged ≥18 years and ≥13 months of continuous enrollment	Mean annual cost increased 35%, from $11,178 USD in 2012 to $17,060, mainly because of a 48% increase in the cost of insulin and a 48% increase in the cost of diabetes technology
			The study indicates that the cost of type 1 diabetes care is driven by mounting insulin prices (9.6% per year) and diabetes technology (also 9.6% per year)
			It is possible that short-term costs will be offset by future savings!
2020, Taiwan	Chen et al. [58]	Cost of illness study from 802,429 adults with newly diagnosed type 2 diabetes identified during 1999–2010 and followed until death or December 2013	Annual health care costs for a male or a female diagnosed with type 2 diabetes <50 years, without comorbidities, antidiabetic treatments, or complications: $281 and $298 USD
			Depression was the costliest comorbidity, increasing costs by 64% and 82%, respectively
			Antidiabetics increased costs by 72–126%
			Costs for retinopathy: 36%
			Costs for heart failure: 49%
			Costs for stroke: 202%
			Costs for the five leading costly nonfatal complications increased by 201–599% for end-stage renal disease, 37–376% for stroke, and 13–279% for limb amputation
			Fatal complications increased costs by 1784–2001% and 1285–1584% for cardiovascular or other causes
			The economic burden of vascular complications and death is compelling over time and the impact of depression cannot be ignored
2020, Netherlands	Janssen et al. [59]	Cost of illness study from 2915 individuals who were classified normal glucose tolerance, prediabetes or diabetes based on fasting and 2-h glucose levels, through resource-use and a quality of life questionnaires	Diabetes costs per individual with diabetes: EUR3006
			Health care costs for individuals without diabetes: EUR1377
			People with diabetes had 2.2 times higher societal costs than people with normal glucose tolerance and lower quality of life
			Total costs were 1.6 higher for people with type 2 diabetes and one complication, and 4.8 higher for people with two or more complications
			Higher age, being female, and having two or more diabetes complications resulted in higher costs and lower quality of life
2020, Scotland	McMeekin et al. [60]	To compare costs for three groups of people with type 2 diabetes: (1) at high risk of cardiovascular disease, (2) without cardiovascular disease, (3) with established cardiovascular disease, and for those with established cardiovascular disease, to compare costs incurred by people with type 2 diabetes with an incident cardiovascular disease, with people who remained incident-free over 3 years from a national diabetes registry	Mean annual costs for people at low cardiovascular risk and without established cardiovascular disease: £2500
			For people at high risk: £3300
			For people with established cardiovascular disease:
			£6900
			Costs for people without an incident cardiovascular event: £2100
			Costs of an incident cardiovascular event: £16,700
			Cumulative costs: £4200 and £21,500, respectively
			Cumulative costs by year 3: £5900 and £25,000
			Cardiovascular disease places a significant financial burden on people with diabetes and the global economy
			The results of the study emphasize the financial consequences of cardiovascular disease prevention strategies

Table 3.1 (continued)

Year and country	Author and reference	Type of study	Results
2020, Sweden	Hellgren et al. [61]	Cost of disease study about the economic and clinical burden associated with poor glycemic control, from a national registry of 77,932 people with type 2 diabetes	People with poor glycemic control
			HbA1c ≥7.0%:19,477 (24.9%)
			HbA1c ≥7.5%: 11,753 (15.08%)
			Even short delays in achieving glycemic control have substantial impact on costs and small effects on life expectancy and quality of life
			Benefits were more pronounced over longer-term horizons and versus longer delays in achieving glycemic control
			For people with HbA1c ≥7.0% and ≥7.5% immediate glycemic control was associated with population-level cost savings of SEK 39 and 38, 50 and 77, and 113 and 107 million, respectively, at 3 and 10 years and lifetime, compared with a 1-year delay in achieving control
			Immediate glycemic control was also associated with improvements in population-level life expectancy of 136 and 118, 467 and 470, and 1305 and 928 years, respectively, in the periods
			Population-level life expectancy also increased to 117 and 129, 915 and 858, and 2590 and 2257 years, respectively
			The economic burden of poor glycemic control in individuals with type 2 diabetes is substantial but could be considered reduced by early and effective treatment to achieve and maintain targets
2021, USA	Khan et al. [62]	Cost of illness study of 17,207 subjects without diabetes 5 years before and diagnosed in 2014 from a commercial claims database	Newly diagnosed patients spent $8941 USD more than control subjects over 5 years, approximately $4828 in the year of diagnosis
			The difference gradually widens over time and is greatest in the year of diagnosis
			The compound annual growth rate is 9% higher
			The rise in medical spending associated with diabetes begins in advance of the diagnosis and supports the need to encourage physicians to implement timely identification and prevention efforts to reduce the economic burden of the disease
2021, Germany	König et al. [63]	Cost of illness study of 325 individuals with diabetes and 4490 people without diabetes from a national health survey for adults	Total excess costs: EUR 927 of which EUR 719 were attributable to direct and EUR 209 to indirect excess costs
			Medication costs were 88% higher and had the largest share in excess direct costs
			Direct excess costs:
			For 4–10 years of diabetes duration: EUR 203
			For diabetes complications: EUR 1405
			Indirect excess costs:
			For >10 years duration: EUR 544
			For high education: EUR 995
			Holistic care approaches like disease management programs might be beneficial for people with type 2 diabetes
2021, Canada	Choi et al. [64]	Cost of illness study from a retrospective cohort study of 41,934 patients with diabetes admitted to seven general internal medicine beds between 2010 and 2015	Compared with patients without diabetes, hospital admissions were more frequent and costly for:
			Soft tissue and bone infections (CAN $8794 vs. CAN $5845)
			Urinary tract infections (CAN $5442 vs. CAN $4427)
			Stroke (CAN $8270 vs. CAN $6992)
			Electrolyte disorders (CAN $4422 vs. CAN $3679)
			Nearly one-third of hospital admissions are related to diabetes
			A preventive strategy focused on reducing hospital admissions secondary to soft infectious complications, stroke, and electrolyte disorders would be cost-saving

(continued)

Table 3.1 (continued)

Year and country	Author and reference	Type of study	Results
2022, Ireland	Sharma et al. [65]	Cost of illness study from secondary data sources	Total diabetes costs: EUR129 million in 2018
			Direct costs: EUR81.5 million, 63% of the total
			Indirect costs: EUR47.5 million, 37% of the total
			Costs per capita
			Direct costs: EUR3994
			Indirect costs: EUR2326
			Potential for cost-effective improvements in type 1 diabetes practices that may reduce the health and economic burden

accounts for most of the indirect costs in middle-income and low-income countries [68]. Substantial regional variations were observed in the economic costs of diabetes: North America had the largest absolute burden, sub-Saharan Africa had the lowest costs, and South Asia was in the middle. High-income countries contribute the most of the economic burden of which 36.5% are indirect costs, and low-income countries bear the lowest burden with an average of 0.7% of GDP [68]. Last but not least, in 2020, the International Diabetes Federation updated its report about global direct diabetes expenditures based on prevalence estimates, United Nations population estimates, World Health Organization health expenditure per capita, and ratios of health expenditure for people with diabetes and without diabetes [68]. The global cost of diabetes for 2019 in adults aged 20–79 years was estimated at 760 billion USD, with 68.7% of the spending on people aged 50–79 years, and is expected to grow to $825 billion USD by 2030 and $845 billion USD by 2045 [68]. Like in previous reports, wide variations in expenditures were observed. The United States has the largest expenditure estimated at $294.6 billion, followed by China and Brazil with USD $109.0 billion and USD $52.3 billion, respectively, and afterwards by Germany (43.8), Japan (23.5), Mexico (17.0), France (16.9), the United Kingdom (14.1), Canada (12.3), and the Russian Federation (10.6) [68]. The main drivers of higher direct costs are poor glycemic control, medications, ambulatory care, hospitalizations, diabetic foot ulcers, cardiovascular disease, end-stage kidney disease, and individual characteristics, including the number of medical visits and the number of comorbidities. In the United States, for example, diabetes costs reached $404 billion USD in 2017. People with diabetes have medical expenditures 2.3 times higher than people without diabetes, accounting for one in four health care dollars. Accurate and comprehensive information on the global economic burden of diabetes will assist clinicians and policy makers in making informed decisions, obtaining resources for activities to prevent or slow its progression, and evaluating the benefits of these interventions [68]. Cost-of-illness studies have been very useful to confirm the increasing economic burden of diabetes at a health-system, national and global level, but do not provide an indication of the value obtained for the money spent [69]. Strategies to analyze the effectiveness of interventions are needed.

Cost-effectiveness of Interventions. Except for politicians and clinicians, it is universally recognized that the economic resources available to meet the demands for health care are limited [70]. Measuring effectiveness in clinical practice should be outcome-oriented, with length and quality of life as the ultimate objectives [70]. Economic analyses are used to describe the costs of health care programs and to ensure that value is obtained for the money spent [71]. The economic analysis of interventions in diabetes started in the 1990s and evolved from economic models to compare the costs and benefits of medications in delaying the progression of advanced complications [72], cost-effectiveness analysis of controlled clinical trials like the Diabetes Control and Complications Trail (DCCT) [73, 74], the United Kingdom Prospective Diabetes Study (UKPDS) [75–81], the Steno-2 Study [82], and comparisons of health care use and costs between real and simulated cohorts of patients with good glycemic control and patients without improvement [83–90].

The evidence collected from clinical trials about intensive therapy has been shown to reduce the risk and advance of diabetes complications [74]. Economic analysis and models have been used to evaluate the cost-effectiveness of intensive therapy for people with type 1 and type 2 diabetes [73–90]. An economic analysis of the DCCT estimated the costs of therapy to be two to three times higher than those of conventional therapy [74]. The results of a Monte Carlo simulation model showed that intensive therapy could reduce 41% the risk of blindness, from 34 to 20%, the risk of end-stage renal disease by 71%, from 24 to 7%, and 43% the risk of amputations, from 7 to 4% [73]. The final analysis compared additional costs from intensive management with savings resulting from preventing or delaying chronic complications: $2000.00 USD per patient with blindness per year, $31,000.00 USD per patient with amputation per year, $45,000.00 USD per patient with end-stage renal disease per year. According to the DCCT, intensive therapy for type 1 diabetes delays 15.5 years in the occurrence of chronic complications and would extend 5.1 years the life expectancy of these patients [73]. Implementing intensive rather than conventional therapy for all the people with type 1 diabetes in the United States would result in a gain of 920,000 years of sight, 691,000 years free from end-stage renal disease, 678,000 years free from lower extremity amputation, and 611,000 years of life at an additional cost of 4.0 billion USD over the lifetime [73]. These were the estimated costs to deliver intensive diabetes care in 1996. The question is if they are affordable in 2022 with the increasing prevalence of type 2 diabetes and the escalating costs of treatment for type 1 diabetes (see below)?

Economic analysis was not initially included in the study design of the UKPDS. However, data were collected throughout the study and were supplemented by cross-sectional surveys of non-patient health care use and quality of life [75]. The evaluations of tight versus less tight blood pressure control [76, 77], intensive versus less conventional blood glucose control [78, 79], and metformin [80] showed that each intervention was highly cost-effective and that all could be provided at modest total costs. Estimation of the cost of all

consultations, visits, hospital admissions, and procedures showed that diabetes complications are associated with substantial immediate and long-term health care costs, not only in the year in which an event occurs but also in permanently raising the average level of inpatient and outpatient costs in subsequent years [81]. In the Steno-2 study, an intensified multifactorial approach was compared with a routine multifactorial intervention for 7.8 years in high-risk individuals with type 2 diabetes and microalbuminuria [82]. At the end of follow-up, individuals randomized to intensified therapy survived for a median of 7.9 years longer, and incident cardiovascular disease was delayed by 8.1 years with a relative risk reduction of 45% and an absolute risk reduction of 20% [82]. The risk of nephropathy, retinopathy, and heart failure was significantly reduced in the intensified therapy group [82]. Information on direct health care costs was retrieved from health registries, and the costs in two groups of 80 patients each were compared. No statistically significant differences were found in total direct costs between the two groups during a 21-year follow-up period. In the intensified therapy group, yearly expenses for prescription drugs were higher than in the conventional therapy group, while in contrast, yearly expenses for primary care and hospital admissions were lower in the intensified therapy group. The difference was driven by the increased costs for admissions related to cardiovascular disease [82]. After 8 years, the yearly costs per individual increased steeply in the conventional treatment group but remained unchanged in the intensified treatment group, albeit after 15 years, the yearly costs in the conventional treatment group started to increase [82]. The results of the study reflect that cardiovascular disease and mortality are delayed by about 8 years in the intensified therapy group, which increases life expectancy by 7.9 years and postpones the occurrence of cardiovascular disease by 8.1 years [82].

Simultaneous reports about the benefits of improving glycemic and overall diabetes control confirmed that they were cost-saving and cost-effective. A historical cohort study conducted in 1992–1997 in a health maintenance organization from the United States showed that mean total costs were $685 to $950 USD less each year in the improved cohort for 1994–1997 [83]. Cost savings in the improved cohort were statistically significant among patients with higher baseline HbA1c levels, and beginning in the year following improvement, the use of services was consistently lower in the improved cohort [83]. In England and Wales, a summary of characteristics of patients with type 2 diabetes from the National Diabetes Audit was used to assess the impact of achieving treatment targets for HbA1c, total cholesterol, and blood pressure on clinical outcomes and health care costs across general practitioner practices [84]. Using the UKPDS Outcomes to estimate long-term health outcomes and health care costs, achieving HbA1c, cholesterol, and blood pressure targets led to a lower incidence of diabetes-related complications, in addition to 0.4–0.6 QALYs and 0.6 years of life gained over a lifetime for each additional target met [84]. The projected health care cost savings arising from fewer diabetes complications as the result of achieving one, two, or three targets compared to none were £859, £940, and £1037 over a patient's lifetime. Interestingly, a typical patient in the lowest-performing decile was projected to gain between 201 and 231 years of life if all patients achieved all three targets [84].

The cost-effectiveness analysis of a hypothetical cohort of people with type 2 diabetes showed that the incremental cost-effectiveness ratio for intensive glycemic control was $41,384 USD per QALY; for intensified blood pressure control, the cost-effectiveness ratio was −$1959 USD per QALY; and the cost-effectiveness ratio for reduction of serum cholesterol level was $51,889 per QALY and increasing with age [85]. Individualized control is cost-saving, primarily due to lower medication costs and decreased life expectancy due to an increase in complications, but also produces more QALYs due to fewer episodes of hypoglycemia and medications [86].

The Evidence about Cost-Effectiveness in Diabetes Management. Starting in 2000, 2010, and 2020, three systematic reviews in which diabetes interventions were stratified confirmed their positive impact in the following categories: (1) clearly cost-saving, including preconception care, intensive hypertension control with ACE inhibitors or angiotensin receptor blockers to prevent end-stage renal disease, comprehensive foot care and patient education to prevent and treat foot ulcers, telemedicine for diabetic retinopathy screening compared with office screening; (2) clearly cost-effective interventions included intensive lifestyle interventions to prevent type 2 diabetes, universal opportunistic screening in high-risk populations, intensive glycemic control (targeting HbA1c <7%) as implemented in the UKPDS study, multicomponent interventions involving behavior change/education and pharmacological therapy for hyperglycemia, hypertension, dyslipidemia, microalbuminuria, nephropathy/retinopathy, secondary prevention of cardiovascular disease with aspirin, early detection of complications and bariatric surgery for individuals with type 2 diabetes, statin therapy for secondary cardiovascular prevention, diabetes self-management education and support, counseling and treatment for smoking cessation, screening every 3 years for type 2 diabetes, integrated, patient-centered care, self-monitoring of blood glucose three times per day among people using insulin, intensive glycemic management for type 2 diabetes, collaborative care for depression [87–89]. The last frontier in cost-effectiveness analysis is the estimation of the health utility impact of diabetes complications [90]. Neuwahi et al. combined the Health Utilities Mark 3

data on 15,252 patients with type 2 diabetes from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Look AHEAD (Action for Health in Diabetes) trials, classified complications and estimated utility decrements [90]. The largest, statistically significant health utility decrements reported were for stroke, amputation, congestive heart failure, dialysis, reduced glomerular filtration rate, angina, and myocardial infarction [90]. Health utility estimates can be used to improve population-based models and to inform policy makers about the benefits, costs, and cost-effectiveness of type 2 screening, prevention, and treatment programs [90].

The Economic Burden of the Disease on Persons with Diabetes and Their Families

The opening statement of the classic article by Ed Wagner's group about chronic disease is probably one of the few "permanent paradigms" in medicine, and an inescapable truth: "in chronic illness, day-to-day responsibilities (including costs) fall most heavily on patients and their families" [91]. The indirect and intangible costs of diabetes are underestimated, their burden increases over the years, and comorbidities impose additional charges. The costs of chronic care, for cardiovascular diseases and cancer, are becoming a serious burden for patients [92]. Diabetes is not an exception, and patients are increasingly suffering signs of financial strain as out-of-pocket costs ascend [92]. The burden of financial hardship from medical bills among individuals with chronic disease results in financial distress, food insecurity, and cost-related medication nonadherence [93], but it is largely unaccounted for in the analysis of diabetes costs. Berkowitz et al. published the results of a cross-sectional analysis of data from 9696 individuals with a variety of chronic diseases including diabetes, in which 23.4% reported cost-related medication underuse, 18.8% reported food insecurity, and 11.0% reported both [94]. The high overall prevalence of food insecurity and cost-related medication underuse highlights one of the main barriers to successful diabetes management [94], but these realities are vetoed in academic forums, where the advantages of new and costly medications are championed regardless of their costs. The ugly reality has to be recognized and addressed: national spending on glucose-lowering medications among adults with diabetes increased 240% by $40.6 billion from 2005–2007 to 2015–2017 in the United States of which insulin and noninsulin medications contributed $26.6 billion (169%) and $12.0 billion, respectively [95]. For insulin, the increase was mainly associated with higher expenditures from analogs (156%); for noninsulin medications, the increase was the result of higher costs of new medications (88%), while the cost of older medications decreased by 34% [95]. Most importantly, the increase in insulin spending came from higher costs per user (out-of-pocket costs) [95]. Having to use multiple insulin doses, the status of people with type 1 diabetes is more alarming [57]. A retrospective analysis of direct costs for children and adolescents with type 1 diabetes showed that mean annual costs increased from $11,178 USD in 2012 to $17,060 USD in 2016, driven primarily by the increase in the costs of insulin, from $3285 USD to $6255 USD, and technology, from $1747 USD to $4581 USD [57]. The authors of this study conclude that the short-term burden of costs could be offset by future savings and that cost-effective analyses should be undertaken to support optimal care [57]. The bottom line is that within 5 years, the direct costs for children and adolescents with diabetes increased by 34.5%, or 7% per year, by comparison with the average annual inflation rate of 1.96% [57]. As already mentioned, the costs of insulin were mainly responsible, increasing by 52.5% in 5 years, or 10% per year!

Considering the acute and long-term health risks of poor glycemic control, it is vital that people with type 1 (and type 2) diabetes have uninterrupted access to insulin (and antidiabetics), yet millions of people with diabetes around the world still struggle to procure medications [96]. Patients are clearly aware of and conceptualize the experience of being without insulin as a "life or death" emergency and have described multiple insulin access barriers including unaffordable health care, institutional unresponsiveness, and personal life transitions [96]. In the face of these adversities, patients resort to several strategies, including omitting medications, asking for lower-priced medications, or self-treatment [97, 98]. Unable to consistently rely on the health care system to facilitate insulin access, patients turn to non-traditional and dangerous alternatives [96]. The negative consequences of these actions have been confirmed but are inexorably linked to the preeminence of social determinants of health in the continuity of diabetes management over a lifetime. The situation is even worse in many low- and middle-income countries which are unable to provide "comprehensive diabetes care" established by international guidelines, and consequently, diabetes care is delivered at a minimal level [99]. To address this reality, Gregory et al. developed a 30-year type 1 care model that looked at the onset of complications, mortality, financial costs, and quality-of-life measures associated with achieving HbA1c levels for "minimal" and "intermediate" care in six countries with varying income levels and geographic locations (Mali, Tanzania, Pakistan, Bolivia, Sri Lanka, and Azerbaijan) [99]. Minimal care was defined as receiving human insulin once or twice per day, two syringes per week, routine clinical care and hospital admissions, and no screening for complications [99]. Intermediate care consisted of a basal bolus regimen for human insulin delivery, 2–3 capillary blood glucose testing per day, point-of-care HbA1c test-

ing, screening for complications, diabetes education, and 24-h emergency call services [99]. The expected outcome for minimal care was an HbA1c range of 12–14% and from 8.0 to 9.5% for intermediate care [99]. According to their model, the cumulative 30-year incidence of complications was much lower for "intermediate" care than "minimal care" [99]. For many people with diabetes all over the world, even intermediate diabetes care is inaccessible or unaffordable.

Conclusions Achieving glucose, cholesterol, and blood pressure targets in patients with diabetes leads to substantial gains in clinical outcomes, a lower incidence of diabetes complications, and quality-adjusted life years (QALYs). Randomized clinical trials significantly increase direct costs but substantially reduce the risk and cost of complications and increase the time free of complications. Underlying factors driving the rising costs of diabetes include deficiencies in health systems, changing demographics associated with increased life expectancy and aging, and the persistence of the status quo. Simmons and Wenzel accurately claimed that in many cases, diabetes inpatients are a case of lose, lose, lose [35]. Health systems unable or unwilling to reinforce multidisciplinary outpatient management can only expect to see increases in the financial and health burden of preventable hospitalizations [36]. To make matters worse, many patients with diabetes struggle to pay medical bills or to pay them at all. To reduce the out-of-pocket costs of prescription drugs, patients resort to several strategies including self-treatment, avoiding taking medications, or asking doctors to prescribe lower-priced medications with negative consequences for their health. Clinical trials have shown that diabetes interventions are cost-saving or cost-effective; achieving these results in the real world is a great challenge. Albeit limited in scope, the study of diabetes costs confirms the increasing impact of the disease on people with diabetes, their families, national health systems, and societies, and represents a call for action to respond in a comprehensive manner to all phases in the natural history of the disease at the prevention level (primary and secondary), at the health care level, and stress the importance of improvements in disease management. The crisis of diabetes costs is worsening; the time to act is now [100].

Multiple-Choice Questions

1. Value of health care is defined as:
   (a) Health care at the highest cost
   (b) Health outcomes appreciated by pharmaceutical companies
   (c) Health outcomes appreciated by physicians
   (d) **Health outcomes achieved per dollar spent**
   (e) Health outcomes achieved per dollar saved
2. The true value of health care can be assessed:
   (a) Only if clinical outcomes are considered
   (b) Only if economic outcomes are considered
   (c) Only if patients' outcomes are considered
   (d) None of the above
   (e) **All of the above**
3. Health economics is about
   (a) Getting better value from the deployment of endless resources
   (b) **Getting better value from the deployment of scarce resources**
   (c) Learning about the use of economic resources
   (d) Saving resources at all cost
   (e) The use of resources to obtain the most advanced technology and medications
4. Opportunity costs are defined
   (a) **As benefits sacrificed for the best alternative**
   (b) As benefits obtained for the most expensive alternative
   (c) As benefits obtained for the most clinically effective alternative
   (d) As risks avoided for the best alternative
   (e) As risks avoided for the future scarcity of an intervention
5. By comparison with people without diabetes, direct health care costs in people with diabetes
   (a) Are equal
   (b) Are lower
   (c) Are one time higher
   (d) **Are two to three times higher**
   (e) Are ten times higher
6. Out-of-pocket spending:
   (a) Is higher in developed countries
   (b) Is the same all over the world
   (c) Is lower in low-income countries
   (d) **Is higher in low-income countries**
   (e) Is irrelevant
7. Indirect medical costs include:
   (a) Medical visits, medications, hospital admissions
   (b) **Patients and family expenditures**
   (c) Years of life lost, loss of opportunity for spouses and children
8. Direct medical costs include:
   (a) **Medical visits, medications, hospital admissions**
   (b) Patients and family expenditures
   (c) Years of life lost, loss of opportunity for spouses and children
9. Intangible medical costs include:
   (a) Medical visits, medications, hospital admissions
   (b) Patients and family expenditures
   (c) **Years of life lost, loss of opportunity for spouses and children**

10. Cost-effectiveness analysis is defined as:
    (a) All the costs required to achieve a clinical outcome
    (b) **Analytical and mathematical procedures supporting an intervention**
    (c) Total costs to achieve a unit of life saved
    (d) Total costs to achieve a unit of quality of life
    (e) The cost to achieve a medical outcome as appraised by clinicians

Glossary[1]

Cost The value of resources engaged in a service.

Cost-benefit analysis An analysis to consider the economic and social costs of medical care and the benefits of reduced loss of net earnings for preventing death or disability. A method for comparing the value of the outcome of all resources consumed (costs) by an intervention against the value (benefits) of the outcome.

Cost-effectiveness analysis A method designed to assess the comparative impact of expenditures on different health interventions. Identifying, measuring, and comparing the significant costs and consequences of alternative interventions to determine the degree to obtain the desired objectives or outcomes.

Cost-effectiveness ratio A comparison between alternatives, the difference in cost divided by the difference in effectiveness.

Cost-utility analysis Economic evaluation in which the outcomes of alternative interventions are expressed in single "utility-based" units of measurement. The most appropriate approach when quality of life is an important outcome.

Direct costs Diagnosis and treatment costs borne by the health system, the community, and patient families.

Health economics Monetary or humanistic trade-offs between wants, needs, and the scarcity of resources to fulfill these wants.

Incremental costs Difference between marginal costs of alternative interventions.

Indirect costs Lost productivity caused by disease to the individual, the family, the society, or the employer.

Intangible costs Costs of pain, grief, suffering, loss of leisure time, years of life lost.

Outcomes The results and value of medical interventions. Multidimensional and dependent on three perspectives: clinical, economic, patients'. The true value of health care interventions can only be assessed if all three dimensions of outcomes are measured and considered.

Pharmacoeconomic research Identification, measurement, and comparison of costs (resources consumed) and consequences (clinical, economic, humanistic) of pharmaceutical products and services.

Pharmacoeconomics Description and analysis of the costs of drug therapy to health care systems and society.

Quality-adjusted life years Adjustment measure that reduces life expectancy, reflecting the existence of chronic conditions causing impairment, disability, and/or handicap as assessed from health surveys, hospital discharge data, or others.

Total costs All costs incurred in producing a set of services.

[1]Modified from [101–103].

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The Ecological Approach to Self-Management in Diabetes

4

Edwin B. Fisher, Paul Bloch, and William Sherlaw

Whether our lives are directed by events around us or events within us, "not in our stars, but in ourselves,"[1] is of concern not only in ethics, aesthetics, law, or religion (the Old Testament of laws and the New Testament of "faith as a mustard seed"[2] within us) but also, of course, in behavioral science, biology, and health. The present paper emphasizes the importance of "events around us," of ecological, social, organizational, community, and policy contexts in health and health behavior. It also describes social, community, and policy approaches to addressing contexts and considers all of these with reference to the challenges of diabetes prevention and management.

[1] Shakespeare, *Julius Caesar,* Act 1, Scene 2.

[2] *Gospel According to Luke*, Chapter 17, verse 6.

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Broad Patterns of Social and Ecological Relationships with Health

Connections between contexts and health are many and often manifest as health disparities. Since the middle of the twentieth century in many high-income countries, smoking has evolved from a privilege of the well-to-do to a problem among those who are poorly educated, poorly paid, and/or burdened by a variety of personal and psychological problems such as depression, schizophrenia, or divorce [1]. In the United States, African Americans, Latinos/as, and American Indians are about twice as likely to have diabetes as the rest of the population. Internationally, infectious diseases, especially HIV/AIDS, are much more prevalent in poor nations and, within all nations, among poor people. Diabetes, along with other noncommunicable diseases, is also socially stratified. Socioeconomic factors, along with the production, marketing, and drawing profit from the sale of food, all contribute to the sharply increasing levels of obesity both within the United States and globally [2]. At the same time, health problems can have enormous impacts on the social and economic environment, as shown by the impact of HIV/AIDS in many countries in Africa. Most recently, of course, worldwide COVID has wreaked its greatest impacts among groups and countries with the fewest resources. By affecting most people with other health vulnerabilities, it has revealed those vulnerabilities and the contextual factors, including poverty and racism, that lie behind much vulnerability.

The "social determinants of health"—the circumstances in which people are born, grow up, live, work, and age have received great attention in recent decades. Differences in health may be revealed and characterized through statistical analysis linking health and illness, disease and death, to latent variables of social inequity such as income, education, and socioeconomic status. Social gradients show that higher levels of income, education, or social economic status are associated with better health status and lower levels of mortality and morbidity across a range of diseases.

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Along these gradients, causality may occur in both directions, such that poor health may also lead to lower socioeconomic status, income, or education, so-called "health selection." Nevertheless, the overriding tendency and bulk of evidence tend to show that social position determines population health status. For this reason, we may speak of social determinants of both health inequities and health status.

Cross-national analyses support the view that disparities in health reflect variability in the socioeconomic characteristics of countries [3]. Michael Marmot's analysis of this global variability in health extends, however, beyond socioeconomic status *per se*. For example, the populations of the United States, Greece, Costa Rica, and Cuba have life expectancies ranging from 76.5 years (Cuba) to 78.1 years (Greece). However, their 2016 GNPs in US dollars range much more widely, from $7815 per person (Cuba) and $11,825 (Costa Rica) to $57,808 (US) [4]. Marmot interprets such data as indicating that, along with income poverty and material conditions, other social factors must also play roles in the development of health risks and the paths of infectious disease transmission. Key social determinants include stress, early life circumstances, social exclusion, unemployment, poor education, a lack of social support, and various addictions [5]. If obesity and other risks such as smoking and hypercholesterolemia and hypertension are the proximal biological causes of noncommunicable diseases, then these social determinants are among the "causes of the causes" [5]. Attention to these poses the possibility of reducing the population's disease burden.

Articulating a Broad View of Experience and Environment: Ecological Perspectives

Before considering social, community, and policy determinants of health and avenues for its betterment, it is helpful to consider broad conceptual models of how contexts, biology, and behavior all influence each other and our health. Certain approaches underline the importance of proximal factors (lifestyles and behaviors), while others place greater emphasis on distal fundamental or structural determinants such as socioeconomic conditions [6]. Whitehead and Dahlgren, for instance, famously represent "the main determinants of health as a set of concentric arcs around the individual" [7]. Health is represented as "the outcome of a web of social influences" [8].

In ecological approaches [9–11], the behavior of the individual is viewed as guided by layers of influences, including the family, proximal social influences such as social networks or neighborhoods, organizational influences such as worksite or community systems or health care systems, and larger social influences such as government, policy, or large economic structures.

Different models may specify different layers of influence and different components of each, but they share two important emphases: (1) that the behavior of the individual reflects the influence of all the layers; and (2) that the layers interact in their influence so that, e.g., communities may influence families, but families may also influence communities [12].

Habitually there has been a tendency to think of social determinants of health acting at different levels in a cascade, with the distal impinging on intermediate factors and finally on individuals through proximal factors. But as Krieger has argued, it is important to understand that interventions at nonadjacent levels may have direct impacts. A new national law restricting or granting rights or cutting or attributing welfare taken at the macro-governmental level may have immediate implications for individuals subject to it. Furthermore, different factors may operate at different levels simultaneously in consort. This is especially evident in the case of the accumulation of disadvantages within vulnerable or marginal groups and individuals. The same factors may differ in their impact at different moments in the life course, and unexpected effects may emerge. Such impacts on health and well-being do not occur in a vacuum but are mediated through the wielding of political and economic power. Discussing Pierre Bourdieu's rich but complex sociology, Ghassan Hage speaks of a "political economy of being" [13]. We may consider that different groups and individuals through social, economic, and cultural capital may have the possibility to deploy their social being to a lesser or greater extent. Here lies the real meaning of accessibility for disabled people, for example. When services and resources in the community are less easily accessible, it will be difficult for disabled people and indeed other marginal groups to fully deploy their social being, that is, to be able to exert choices which they value. Such capabilities, defined as "the substantive freedoms" a person "enjoys to lead the kind of life he or she has reason to value" [14], are dependent on political and economic power, which both enables and obstructs the choices of groups and individuals.

Relationships Among Influences: The Example of Genetic Expression and the Environment

Gene-environment interactions illustrate well how interactions among levels of ecological models are fundamental to health and well-being. Many think of genes as causes that obviate other influences on behavior. Old controversies as to whether one or another condition, e.g., schizophrenia, is ***either*** genetic ***or*** learned presumed that the one trumps the other. The reality is that genetic, other biological, behavioral,

and environmental variables interact in complex ways to lead to behaviors and health states [15].

The importance of the environment in determining whether or not a gene will have any effect is illustrated in the work of Michael Meaney and his colleagues with rat pups and their dams. It turns out that the frequency with which rat dams lick their pups and other maternal behaviors influence the expression of genes related to stress response in adults. "Epimutations" (specific changes in methylation of cytosines on genes) mediate the relationship between rearing and adult stress response [16]. A large number of studies by Meaney and his colleagues and other groups show that this epigenetic structuring of gene expression is the result of a series of intracellular processes that can be set in motion by external contextual influences such as maternal nurturance [17]. The expression of a cell's genes is thereby dependent on the environment within the cell, an interdependence between genes and the intracellular environment that sets a model for gene X environment interactions at the levels of whole animals and populations.

The role of central nervous system serotonin in cardiovascular disease illustrates well the complexities surrounding gene X environment interactions. As contributed to and summarized by Williams and his colleagues [18, 19], there is considerable evidence that long and short alleles of the serotonin transporter gene promoter polymorphism appear to affect CNS serotonin activity in ways that impact CVD risk. But this is not a simple relationship in which, for example, one or the other allele lowers serotonin and raises CVD risk. Among Rhesus monkeys reared by their parents, for example, there is no difference between those with long and short alleles in CNS serotonin levels. However, among those reared among peers, the short allele is associated with reduced CNS serotonin and greater risk [20].

Socioeconomic and social factors surely influence the pathways from the serotonin transporter gene to CVD risk. For example, overstressed parents or neighborhood crime may be analogous in humans to the levels of a rat dam's nurturance or to the peer vs. parental rearing that moderates gene expression in monkeys. There are also several broad contextual factors that influence the pathway from genotype to CVD risk. The prevalence of the long-allele genotypes varies by country of origin, from less than 30% in China and Japan to over 70% among populations originating in Africa [21].

But what is most interesting and most illustrative of the complexities of gene X environment interaction are perplexing inconsistencies regarding the serotonin transporter gene. It turns out that the same genotype can have both advantageous and disadvantageous effects. In some studies, the long alleles are the "bad actors" [22, 23]; those with one or two long alleles have significantly greater blood pressure responses to stress and greater CVD risk. However, in a longitudinal study of depression among young adults, the number of *short* alleles (either one or two) was related to greater likelihoods of depression and suicidality [24].

If we think of genes as conferring a simple advantage or vulnerability to some disease or condition, it is confusing that a particular genotype is associated with benefit in some studies and vulnerability in others. Williams and his colleagues have suggested another way of framing these influences as conferring a greater or lesser *sensitivity* to environmental influences [19, 25]. Thus, in a study of depression among young adults, those with two short alleles of the serotonin transporter gene reported greater depression than those with other genotypes *if* they had been exposed to early adversity in childhood or recent negative life events. Among those exposed to a positive early environment or recent events, on the other hand, those with two short alleles reported the least depression [26]. It seems that the two short alleles confer no advantage or disadvantage, *per se*, but greater responsiveness to the environment, for good or ill.

Others have noted a similar pattern of greater sensitivity to the environment. In one study, observers' measures of poor home and neighborhood quality during adolescence predicted lower self-esteem in young adulthood among those with short alleles. In contrast, there were no effects on home and neighborhood quality among those with two long alleles [27]. In a study of those exposed to a series of hurricanes in Florida in 2004, county-level indices of joblessness and crime moderated the effects of the transporter gene in a remarkable interaction. In counties with high crime/high unemployment, the short allele was associated with higher levels of post-traumatic stress disorder, but in counties with low crime/low unemployment, the short allele was associated with lower risk of post-traumatic stress [28]. Putting these findings together, it seems that short alleles confer greater sensitivity to environmental influences, either positive or negative. That is, sensitivity to the environment may be, itself, influenced by genetic variation. Thus, the genotype is far from destiny, independent of context. Rather, sensitivity to context is itself embedded in some genotypes—no doubt further influenced by other contexts in the external, phenotypic, and intracellular environments.

What Meaney and Williams and their colleagues point out at the level of the cell is parallel to what others have called "reciprocal determinism" [29] in the relationships between human behavior and its environmental surroundings. Just as the cell phenotype acts as an environment that influences the expression of the cell's genetic material and the further emergence of the cell's phenotype, our environment governs our actions, which, in turn, exert influence on the environment that will govern our next actions. Continuing up the ladder of complexity, one can see the same kind of reciprocity in the influence of:

- the group on the individual and the individual on the group

- the organization on the division and the division of the organization
- policies on organizations and organizations on policies.

This pattern of the reciprocal influence of surround on agent and of agent on surround appears to be an important dynamic across living systems. It poses an important counterpoint to more primitive models such as those which get lost in the debate over whether genes ***or*** environment are important, models that seek a single cause, and in which a single thing can be only a cause or an effect but not both.

The Illusion of the Fundamental.

It is worth noting that we can see either party to a reciprocal relationship as fundamental. We might say the work unit is the fundamental determinant of employee performance as moderated by the organization, or we might say that the organization is the fundamental determinant, as moderated by the work unit. Both may be equally true. Both illustrate the illusion of "fundamental" amidst the reality of multiple, multilevel, interacting determinants. Diabetes provides a classic example. Pima Indians in the United States show "the highest prevalence of type 2 diabetes mellitus…of any population in the world" [30]. Yet, Pimas living in Mexico have relatively low levels of diabetes. Ample evidence links genetics to diabetes *within* the Pima population [30]. Thus, the relationships among genes, environment, and diabetes among the Pimas can be stated in either of two ways:

- Genetic factors associated with membership in the Pima population have a strong influence on the prevalence of diabetes among a population exposed to the obesigenic environment of US diet and food distribution
- The obesigenic environment of the United States has a strong influence on the prevalence of diabetes among a population such as the Pima, who are genetically predisposed to high rates of diabetes

Genetics as a Model for Analyzing Social and Ecological Influences

In genomics, causal relationships are frequently identified through cluster analysis and related statistical techniques that compare differences in probabilities of hundreds or even thousands [31] of genes among those with varied phenotypes. In such analyses, no one gene is the cause or indicator of the phenotype. Instead, the relationship between phenotype and all the genetic markers in the analysis is probabilistic, not all or none.

This approach to characterizing genetic influences is descriptive but persuasive as to the likely causal relationship between profiles and outcomes. To what extent does it provide a model for making judgments about causal influences in a multilevel approach to complex behavior, such as might be arrayed by genetic, personal, social, organizational, and geographic influences?

From the perspective of the individual, we can envision complex webs of influence including genetic and other individual characteristics as well as, outside the individual, the ecological layering of family, neighborhood, community, worksite, government, and policy, all arrayed in a spatial analysis. These multilevel complexes could be examined as they explain, for example, the likelihood of smoking and its relationship with rates of cardiovascular disease and cancer, or BMI and its relationship with diabetes, obesity, and other related diseases.

Ecological Analysis and Diabetes

Consider adults with diabetes. Even if they spend 6 h a year in a professional's office—certainly more than average—that still leaves over 8760 h a year they are "on your own." The ecological perspective provided a basis for program planning for the Diabetes Initiative of the Robert Wood Johnson Foundation, which demonstrated the successful implementation of diabetes self-management programs in "real world," ethnically and economically diverse primary care and community settings around the United States [32, 33]. To guide program development across 14 different project sites, an ecological perspective was used to identify the resources and supports for self-management that people with diabetes need to take care of their disease in their daily lives. These include (1) continuity of quality clinical care, (2) individualized assessment, (3) collaborative goal-setting, (4) opportunities to learn skills both specific to diabetes (e.g., measuring blood sugar) and for addressing challenges, including negative emotions, that may interfere with management, (5) ongoing follow-up and support, and (6) community resources such as for regular physical activity and a healthy diet [32–34]. The last two, ongoing follow-up and support, and community resources, especially illustrate the contributions of an ecological perspective to diabetes management.

Sustaining Health Behaviors: Follow-Up and Support

Sustaining diabetes self-management is of key importance. We all have great respect for intervention studies that include follow-ups for 1, 2, or 3 years. Consider now that the average

individual with type 2 diabetes will live 20, 30, or 40+ years with the disease. How do we make the extension from studying the maintenance of change over a year or 2 to developing systematic ways of supporting individuals who need to maintain changes for decades?

Major guidelines [35] of the American Diabetes Association, American Association of Diabetes Educators, and the American Dietetic Association distinguish between diabetes self-management education, the results of which often deteriorate by 6-month follow-up, and diabetes self-management support to "assist the individual…to implement and sustain the ongoing behaviors needed to manage their illness." This reflects reviews in diabetes self-management that showed that the length of time over which intervention is maintained is the best predictor of changes in blood sugar control [36].

The importance of sustained contact is not limited to diabetes. It was recognized, for example, in early meta-analytic reviews of research on smoking. In their 1988 review, Kottke and colleagues noted that "Success was…the product of personalized smoking cessation advice and assistance, repeated in different forms by several sources over the longest feasible period" [37]. More recent reviews have continued to document the importance of duration of the interventions in smoking cessation [38]. In research on weight loss and weight management as well, the duration of interventions emerges as a key predictor of success [39–41].

The *Diabetes Initiative* of the Robert Wood Johnson Foundation came to recognize that the most important characteristic of type 2 diabetes and self-management of it is that it is "for the rest of your life" [42]. It sounds simple, but it is striking how this consideration reframes thinking about self-management programs. As an example, consider the goals of working with a 45-year-old adult whose diabetes is under poor control. Is the goal to get that control improved in the next 3 months? Or, is the goal to establish an approach to living with diabetes that will help the individual attain the best possible control over the next three or four decades? Does the choice of goal have implications for the approach to helping the individual? Clearly, the lifespan is an important context of behavioral medicine and one we are just beginning to grasp [43].

In 1968, early leaders in the field of behavior modification, Donald Baer, Montrose Wolf, and Todd Risley noted that maintenance of behavior changes needed to be arranged or planned, as they put it, to be "programmed rather than wished for or lamented" [44]. A December 2021 search of PubMed for papers with "diabetes" (or "diabetic") and self-management in their titles or abstracts yielded 6536 responses. A subsequent search with these terms and cognates of "sustain" or "maintenance" yielded only 782, 12.0%.[3] A parallel search just of "self-management" yielded 22,931 while that with "self-management" as well as cognates of "sustain" or "maintenance" yielded 2776, again 12.1%. Clearly, a major challenge remains the relative dearth of research on maintaining or sustaining changes brought about by self-management.

From the perspective of "programming" maintenance of behavior, contexts take a central role. Behavior will be sustained to the extent that the daily lives of individuals provide opportunities for the behavior, facilitate it, and reinforce it. It is the contexts of neighborhoods, workplaces, communities, families, and friends that must sustain the healthy behaviors that prevent or manage the disease and enrich lives.

The content of follow-up may include continued assistance in refining problem-solving plans and skills, encouragement in the face of challenges, assistance in responding to new problems that may emerge, and assistance that may entail linking patients back to primary care providers or other parts of the disease management team. The Diabetes Initiative grantees identified a number of strategies for providing follow-up and support [42], including nurse follow-up by telephone [45–50] as well as through community health workers, lay health workers, *Promotoras*, or health coaches [51–54].

The structure of clinical care may also contribute to ongoing support through group medical visits [55, 56]. In these, all patients in a particular category (e.g., those with diabetes, cancer survivors, or, perhaps, those with any of several chronic diseases) are scheduled for a group visit in a 2- or 3-h block of time. Physicians and other staff carry out individual medical visits within this group visit that also includes educational and supportive discussions or other activities.

In spite of the importance of sustaining key behaviors, *ongoing* follow-up and support for *good self-management* is not always recognized as an important service. Among those with diabetes, for example, ongoing support for self-management may be made available for those whose indices of blood sugar control exceed some criterion (e.g., hemoglobin A1c > 8%), but not for those who are below that criterion, but to help them maintain their relatively good management. Our systems of providing health care are still slow to recognize what Baer, Wolf, and Risley noted in 1968: that maintenance of changes in behavior "…needs to be programmed rather than wished for or lamented" [44].

[3]Search syntax: ((diabetes [tiab] OR diabetic [tiab]) AND self-management [tiab]) AND (sustain* [tiab] OR maintain* [tiab] OR maintenance [tiab]). Date of search: 29 December, 2021.

Community Resources Access to Healthy Food

An early study examined the distribution of supermarkets and fast food restaurants in St. Louis, Missouri, in the United States [57]. Supermarkets were audited and sorted into tertiles according to their offering of fresh fruits and vegetables and lean, low-fat, and fat-free meat, poultry, and dairy products. Of 21 supermarkets in census tracts with a greater than 75% African American population, none were in the highest tertile. In contrast, 17 of 30 (57%) census tracts with less than 10% of the population below the poverty level and more than 75% white population were in the top tertile.

Do neighborhood resources make a difference? Obesity rates vary between neighborhoods within cities such as New York. A range of factors would seem to be involved, including the presence of supermarkets and food stores and the area's income [58]. Earlier research examined the relationships between obesity and supermarkets and convenience stores in neighborhoods [59]. After adjusting for gender, race, age, income, education, and physical activity, it turns out that the presence of supermarkets in a census tract was associated with a lower prevalence of obesity (prevalence ratio = 0.83 relative to census tracts with no supermarkets), while the prevalence of convenience stores was associated with a higher prevalence of obesity (prevalence ratio = 1.16 relative to neighborhoods with no convenience stores). Those in census tracts with only convenience stores were 1.45 times as likely to be obese as those in tracts with only supermarkets.

This is an area in which the view of self-management as the individual's own responsibility can be especially damaging. The benefits of teaching about physical activity and a healthy diet are compromised if people live in neighborhoods in which it is dangerous to walk alone, in which food sellers offer little healthy food, and with little public transportation to access better resources. Studies indicate that such deprivation of community resources is more common in low-income and minority neighborhoods [57].

The Ecology of Professionals

A critical feature of the application of the ecological model is to recognize that it applies as much to providers as to recipients of care. For example, the network analyses of the influences of social networks and ties on obesity [60], cigarette smoking [61], depression [62], and other features of health and quality of life have been extended to physicians' prescriptions of medications [63]. This leads to recognition of the importance of systems that facilitate good clinical care and professional services, not just the training and commitment of individual providers.

Wagner's Chronic Care Model articulates the organizational and system features that support the integration of Resources and Supports for Self-Management with key components of clinical care [64]. One health system instituted a comprehensive approach to improving a range of diabetes care services, including handouts and manuals, outpatient programs, web-based programs, telephone/nurse case management, financial incentives for physicians' meeting testing guidelines, and patient incentives for annual eye exams. These were followed by improvements in a variety of outcomes [65]. But the emphasis on such integration of comprehensive clinical and self-management services is not widely shared in health care. Audits of health plans utilized by major companies [66] show little support for such elements of care, and 60–70% of patients with diabetes report not having received self-management interventions [67].

Another ecological approach to systems of care is the patient-centered medical home (PCMH). A review of evaluated demonstration projects showed encouraging evidence for the benefits of PCMH in diabetes care [68]. At the organizational level, the PCMH includes resources such as electronic medical records, evidence-based algorithms and care plans, and ties to referral sources and other community-based resources for patients. In many presentations of the patient-centered medical home, the interdisciplinary, collaborative team—i.e., the social or organizational level of the ecological model—is emphasized as its central characteristics.

A Social Strategy: Peer Support

The chapter now turns to three areas of the application corresponding to three key levels of the ecological model: the social, community, and policy levels. At the social level, peer support programs—known by varied terms, e.g., "community health workers," "*promotores de salud*," "lay health advisors," "health coaches"—are widespread and supported by a diverse literature [69–75]. There are many ways in which peer supporters can encourage health. Among these are helping individuals sustain important health behaviors.

Peer support is an especially promising approach to providing ongoing support for disease management and sustained changes in health behaviors, such as smoking cessation and weight management. To begin, peers have time, a critical ingredient in all of health care [76]. Whether volunteer or paid staff, nonprofessionals trained to assist and encourage ongoing efforts at disease management and prevention can also be readily available to those they help and spend time with them to get to know them and their circumstances.

Additionally, the credibility of peers' assistance is enhanced by being "like me." Research shows that individuals rely on experts to understand what is important and set

priorities, but turn to peers and "peer coping models" [77] to gain confidence that they, themselves, can implement a plan. Adding to their credibility, peer supporters oftentimes have the advantage of having the health problem with which they are assisting. Also, they often come from similar neighborhoods, so they share the perspectives and experiences of those they are seeking to help.

Extending the advantages of time and similarity, peer supporters can work with individuals on the details of implementing important health behaviors. For example, it is one thing to set an objective of physical activity for 150 min a week. It is another thing to work out exactly what activity, where and how often, and how an activity will fit in with other responsibilities and daily routines. In a report of qualitative analyses of peer support aptly titled "*Teaching How, Not What*" [54], a participant noted that, whereas her doctors and nurses helped identify *what* to do, her peer supporter "taught me a lot about *how* to control my diabetes, *how* to eat healthy, and *how* to do my exercise" (emphases added).

A 2014 review in the *Annual Review of Public Health* [78] identified the contributions of community health workers to basic health needs (e.g., reducing childhood undernutrition), to primary care and health promotion, and to disease management. Another review [79] included peer support interventions from around the world that addressed a wide variety of prevention and health objectives entailing sustained behavior change (in contrast to relatively isolated acts such as cancer screening). It identified papers from the United States (34 papers), Canada (7), Bangladesh, England, Pakistan, and Scotland (4 each), and Australia, Brazil, Denmark, Ireland, Mozambique, New Zealand, South Africa, and Uganda (1 each). The health issues papers addressed included pre- and postnatal care (17 papers), cardiovascular disease (10), diabetes (9), asthma (6), HIV (6), mental health (8), cancer (4), substance use (3), and chronic fatigue syndrome and chronic obstructive pulmonary disease (1 each). Across all 65 papers, 54 (83%) reported significant between-group or pre-post changes showing the benefits of peer support. Among the 48 papers reporting RCTs, 39 (81%) reported significant between-group or pre-post changes. The review also included a summary of 19 other reviews of peer support interventions. Across these 19 reviews, a median of 64.5% of papers reported significant effects of peer support.

Nineteen papers reviewed provided pre- and post-intervention measures of hemoglobin A1c (HbA1c) as a measure of glucose control [80–93]. Using the individual publication as the unit of analysis, the average HbA1c declined by 0.76 points (e.g., from 8.76% to 8.00%; $p = 0.001$). In diabetes, a reduction of HbA1c by half a percentage point, e.g., from 8.5% to 8.0%, is generally considered clinically meaningful. The average reduction across these 19 studies of 0.76 points is thus very striking and adds considerably to the evidence for the benefits of peer support in diabetes management [79].

Peers for Progress (peersforporgress.org) is a program at the University of North Carolina-Chapel Hill (led by co-author EF) that is dedicated to promoting peer support in health, health care, and prevention [94]. In 2009, it funded fourteen projects on peer support in diabetes in nine countries—Argentina, Australia, Cameroon (2 projects), China, England, South Africa, Thailand, Uganda, and the United States (5 projects). In addition to effectiveness, the fourteen showed real-world applicability. All were able to be implemented, often in under-resourced settings and/or with disadvantaged populations. Based on data provided in progress reports, the average baseline HbA1c in the fourteen was 8.71%; clearly, the projects were not "cherry picking." Across peer support interventions, projects retained 81.9% of their participants, again quite impressive, especially considering the underserved settings and disadvantaged populations of many of the projects. The average among site reports of reductions in HbA1c was 1.18 points, well above the 0.5-point reduction generally considered clinically meaningful. Other indicators of benefits included reduced hospitalizations [95]. Two years after the end of funding from Peers for Progress, group programs in Uganda and South Africa continued and reported *increased* participation and attendance. Similarly, a private, not-for-profit health care company, adopted the program as routine care for diabetes in all of its U.S. clinical sites [96].

Across 7 of the Peers for Progress sites, documentation of participants' contacts with peer supporters enables analyses of both predictors and effects of contacts. In structural equation modeling, lower levels of available support for diabetes management, higher depression scores, and older age predicted any vs. no contact with peer supporters. That is characteristics indicative of greater need for assistance were associated with greater receipt of peer support. Any contact, in turn, predicted lower levels of final HbA1c. Additionally, no, low, moderate, and high contacts showed a significant linear, dose-response relationship with final HbA1c [97].

Strategic Advantages of Peer Support

Peer support is especially beneficial for people with diabetes with high needs and for those who are hardly reached by conventional health care services. Two meta-analyses have shown an association between higher baseline HbA1c and a larger effect size [98, 99]. Compared to usual care, peer support is an effective strategy for improving glycemic control for underserved, low-income minority populations [100–102]. For example, a program for ethnic minority patients of safety-net clinics in San Francisco reported significantly greater reductions in HbA1c with peer support in addition to

usual care, compared to usual care alone [103]. These benefits of peer support were significantly greater for patients categorized as *low* on medication adherence and self-management at baseline [104]. Similarly, in support exchanged within dyads of US veterans with diabetes, improvements in blood glucose relative to controls were greatest among those with initially low levels of diabetes support or health literacy [85]. In an underserved Chicago population, a low-intensity, home-based community health worker intervention was more effective at decreasing HbA1c among participants that had lower levels of diabetes self-care at baseline [105]. These are important observations: intervention worked across all individuals, but worked especially well relative to controls for individuals whose diabetes management was in most need of improvement (as suggested by various indicators). This pattern of peer support reaching and benefitting those whom we would expect to be most difficult to reach and the benefit was sustained in a systematic review of peer support programs across a variety of health conditions [106]. Therefore, peer support is a viable strategy to address one of the major challenges in population health management: benefitting high-need groups that experience disproportionate burdens and costs of care.

Peer support has also demonstrated strong potential to address diabetes and co-morbidities [100, 107]. The co-occurrence of diabetes and depression is quite common; people with diabetes are twice as likely to be depressed as those without diabetes, and symptoms of depression are present among almost one-third of people with diabetes [108]. Psychological problems, from heightened distress to serious psychopathology, compromise self-management behaviors and exacerbate disease. Among people with diabetes, depression is associated with poor glycemic control and decreased adherence to medical treatments [107]. Peer support directly mitigates depressive symptoms by providing social and emotional support through regular, affirming contacts. Even if recipients of peer support do not change their behaviors, they still experience emotional benefits from having someone with whom to talk [109]. Additionally, peer support addresses diabetes and depression together by helping people with diabetes overcome socioeconomic barriers and teaching common skills to cope with both conditions. Peer supporters can help identify safe places to exercise and ways of buying affordable food, as well as coach people with diabetes to develop healthy coping skills when facing stressful situations and setbacks. For example, a CHW stress management intervention for U.S. Latinos with type 2 diabetes found a dose-response relationship between attendance at stress management sessions and improvements in HbA1c and diabetes distress [110].

In some cases, psychological improvements have been observed as a by-product of peer support programs designed principally for diabetes. With support from *Peers for Progress*, the PEARL project in Hong Kong examined the impacts of peer support on diabetes-related distress [111]. PEARL was designed to assist in diabetes management, not necessarily to reduce emotional distress. At baseline, however, about 20% of participants exceeded norms for depression, anxiety, or stress on the Depression, Anxiety, and Stress Scale (DASS) [112]. Among this 20%, the DASS scores of those randomized to receive peer support were significantly reduced relative to those randomized to control. Among controls, those with elevated DASS scores also experienced disproportionately high rates of hospitalization, whereas those randomized to PEARL showed hospitalization rates comparable to those without elevated DASS scores. Perhaps because of the social support intrinsic to the PEARL peer support intervention, it achieved substantial effects on distress and associated hospitalizations.

Another example of the distress-reducing benefits of peer support is the REACH program, a diabetes lifestyle intervention for African Americans and Latinos with type 2 diabetes in Detroit [113]. Although the intervention was not intended to reduce symptoms of psychosocial problems, it was able to reduce diabetes-related distress by encouraging positive lifestyle changes and coping skills that could be applied to both diabetes and psychosocial challenges.

A Community Strategy: Community Action

Recognition of the diverse types and levels of influence on behavior and health can leave one discouraged as to the possibility of changing such influences as the built environment, culture, or social networks. Surely interventions in such arenas are challenging. Nevertheless, promising approaches have been developed. Here, we focus on broad community campaigns to combat cardiovascular disease (CVD), smoking cessation, and diabetes prevention. These provide models for community approaches to diabetes management but ones that have been too little pursued.

North Karelia: CVD Risk Reduction in Finland

The North Karelia project [114, 115] set a strong example for the incorporation of multiple channels and intervention approaches, from mass media to cooperation with agricultural, dairy, and food merchandising groups to improve the availability of healthy foods such as low-fat milk [114]. Because of unusually elevated cardiovascular disease and risk factors within the region, the program was developed through the Department of Epidemiology of the National Public Health Institute within North Karelia, with field offices at the level of county departments of health and local advisory boards. The project ran in North Karelia from 1972

to 1977 and then was extended to the rest of Finland, with increased national government and policy support, through its formal end in 1997, after 25 years.

Community organizations in North Karelia included collaboration with existing official agencies and voluntary health organizations so that "the new health service activities initiated by the project became part of formal public health activities in the area" [114, p. 166]. In addition to extensive health education materials, mass media interventions interacted with local newspapers, community organizations, and campaigns. Training activities included not only doctors and nurses but also social workers, representatives of voluntary health organizations, and informal opinion leaders. Training was organized through county-level or other local organizations. Training and development of treatment guidelines in the health system included reorganizing screening and treatment for hypertension and care following myocardial infarction. Cooperation with other local organizations included not only the voluntary health agencies but also the critical food industry (e.g., including dairies and sausage factories) and grocery stores [114, pp. 166–167].

Nationwide impacts to which it contributed included an 80% reduction in the use of butter on bread, reduction in the prevalence of smoking among men from 60% to 16% in 2016, sharp decreases in salt intake with corresponding reductions in systolic blood pressure from 149 to 134 mmHg in women and 153 to 127 among men, 20% reduction in serum cholesterol, and an 80% reduction in cardiovascular mortality among men aged 35–64 [115]. In comparison with other parts of Finland, the North Karelia campaign led to significant reductions in cardiovascular risk factors [116] and mortality [117] as well as reductions in cancer risk factors [118].

Two characteristics appear critical in the North Karelia community organization: (1) the variety of activities and channels included, and (2) the attention in all areas to implementation through and in collaboration with local organizations. In a 2020 review of the project [115], its leader, Pekka Puska, and a co-author emphasized its community organization: "…the project catalyzed, trained, and coordinated the work that was carried out by numerous community and nongovernmental organizations" (p. 496). They also emphasized the breadth of approaches the program included: "…far beyond health services and providing health information… practical priority targets of change…provided change skills…social and environmental support…grassroots approach…local community organizations, schools, workplaces…application of lifestyle changes…mass media… television, pamphlets, and newspaper articles…National level health policy and legislation affecting changes in the food industry and tobacco use…" so that "Health had become the conversation of Finland" (p. 498).

Since the days of the North Karelia project, numerous population- and community-based interventions on health promotion and diabetes prevention have emerged in many countries around the world, and important learnings and recommendations for optimizing intervention and evaluation processes have been published [119].

A Danish research group (co-author PB and colleagues) has developed a conceptual framework, the supersetting approach, to integrate the breadth of community resources, including citizens and professional stakeholders, for social action and health promotion. It involves the coordinated engagement of multiple stakeholders in multiple community settings to implement multiple actions at multiple levels [120]. The supersetting approach includes five principles: (1) *context* to ensure that everyday life challenges of citizens and professionals are respected and considered in planning activities, (2) *participation* to ensure that people are motivated to take ownership of processes of developing and implementing interventions, (3) *action competence* to ensure that people acquire skills and competences to express and act on their visions and aspirations, (4) *integration* to ensure that activities are implemented across the boundaries of specific settings, and (5) *knowledge* to ensure that scientific knowledge is used to inform action and produced from the action. Moreover, the supersetting approach includes three highly participatory, structured, and research-based phases: (1) describing the context, (2) developing and implementing the intervention, and (3) conducting the evaluation. These phases have been optimized methodologically through iterative processes of co-creation with citizens, social workers, health professionals, and researchers. Although it is generally acknowledged that complex interventions are difficult to evaluate [121], there is now sufficient evidence from meta-analyses of intervention studies on community engagement to conclude that they may positively impact a range of health outcomes [122].

An important extension of community approaches is their integration with life course perspectives. Type 2 diabetes provides a case in point, as conventional approaches targeting high-risk adults will not efficiently ameliorate this growing disease burden. It is therefore essential robustly to identify determinants across the entire life course and, subsequently, appropriate interventions at every stage to reduce an individual's disease risk [123]. A life course approach has the potential to prevent noncommunicable diseases, from before conception through fetal life, infancy, childhood, adolescence, adulthood, and into older age. Epidemiological research in cardiovascular disease has shown health benefits resulting from the cumulative effects of health behavior over an individual's lifetime, not from a change in lifestyle [124]. On this basis, it is also important to involve children and youth in decisions pertaining to the shaping of the social and built environments of their everyday lives. This was done

within the framework of a large community-based intervention project in Denmark by addressing schoolchildren's perceptions and visions for a socially and physically improved school environment [125]. Guided by an everyday-life perspective and applying participatory action research methods including social imagination and visual techniques, the study observed that children were very capable of articulating their thoughts, ideas, and visions for a better and healthier school environment. Identified challenges and solutions varied widely and represented a broad perspective of health including social, physical, environmental, and emotional aspects. The paper concluded that children can be visionary and creative stakeholders and important agents of change in community development efforts if methods to include them are interactive, participatory, and carefully adapted to the age of the target group. Thanks to the collective dedication and action of schoolchildren, teachers, and management, the aspirations of the children resulted in the commencement of environmental, structural, and organizational change processes, which still continue today, years after project termination [126].

Integrating Community and Peer Support in Shanghai

Community approaches and peer support share a recognition of the importance of social influences around us. Additionally, community approaches offer the potential of expanding the base and organizational resources for peer support and other initiatives. This interplay of peer and community has emerged in work on diabetes management, advanced under the aegis of the "Shanghai Integration Model" [127]. This model brings together specialty/hospital care with primary/community-based care for people with diabetes. This provided the setting for the development of peer support programs in nine community health centers that serve, on average, communities of about 100,000. Peer leaders encouraged those with diabetes to adopt good health habits, which included adherence to prescription medications, a healthy diet, physical exercise, seeking community support for emotional well-being, and attending routine primary and specialty care. They did this by leading neighborhood activities, co-leading meetings on diabetes management, and following up with individuals and families. This resulted in significant changes in HbA1c, other clinical markers, and diabetes distress among 1284 participants from the start of the program to the end of the active program at 12 months. Changes were especially pronounced among those with poor baseline status, e.g., HbA1c reduction from 9.09 to 8.50% among those ≥8% at baseline [128].

Two research staff blinded to outcomes rated each community health center's implementation of the peer leader program. From these ratings, more extensive implementation of the program was associated with reduced HbA1c and diabetes distress and increased neighborhood support. In particular, ratings of the extent to which programs linked with community resources and utilized neighborhood committees were associated with improved HbA1c, indicating the value of peer support programs including community resources.

Summarizing the study of nine Community Health Centers, it showed improvements in clinical and quality of life measures initiated through peer leaders promoting diabetes self-management as part of the Shanghai Integration Model, especially among those with elevated measures at baseline and among those in high implementation sites. However, assessment of the implementation showed that not all centers implemented equally, that level of implementation was related to outcomes, and that engagement of community organizations enhanced impacts. This suggested that a way to address variable implementation among community health centers is to broaden the programmatic base to include community organizations.

Following the strategy of broadening the programmatic base, the current phase includes both health centers and other organizations in the community to bring further support for the program. These include community health promotion offices and citizen-led "Community Self-Management Groups," of which there are more than 5000 in Shanghai. Additionally, support for the program comes from the Shanghai government, which designated peer support as a key strategy for achieving 2030 goals for self-management of diabetes and other chronic diseases.

To evaluate program implementation with this expanded, community base, project records, semi-structured interviews, and an implementation assessment have characterized processes of adaptation of standardized materials, examined the extent to which the program was implemented, and identified key success factors and challenges. Communities took standardized intervention components and adapted them to meet their needs. They also assumed responsibility for the implementation of different components of the program based on their community's available capacity. Additionally, community innovations occurred that were then standardized for dissemination in future iterations of the program. Key success factors included cooperation and collaboration among varied partners within and across communities.

COVID not only interrupted the later stages of the program and delayed the final evaluation but also illustrated the benefit of the community organization approach. With the capacity developed among the collaborating community groups and peer leaders, they were able to assist in the implementation of control provisions within their neighborhoods,

such as by assisting older adults in obtaining food and other supplies, while also maintaining diabetes support activities such as social networking with WeChat, the dominant social networking base in China. Given Community Health Centers' need to focus on clinical management and prevention of COVID, the peer leader program would likely have dwindled without its expansion to include other community organizations. Instead, including other community organizations provided an additional base not only to sustain the diabetes support program but also to assist in pandemic control.

Cigarette Smoking

Although apparently a simple behavior, cigarette smoking illustrates well the broad range of contexts emphasized in this chapter. As detailed in an integrative review in 2004 [1], influences on smoking range from the brain physiology of nicotine addiction to broad economic factors. At the individual level, addiction to nicotine and genetic factors contribute to long-term smoking [129, 130]. Psychological conditioning is also important. The average smoker of a pack a day for 20 years has inhaled over a million times, establishing diverse conditioned associations of smoking with work, relaxation, drinking coffee, and other routines, and various moods like anxiety and depression [1].

Research from Scotland and France [131] shows that people at the lower end of the social gradient are more likely to smoke and smoke longer than those from higher up on the social gradient. However, it is not only social position that will determine whether one becomes a smoker and one's smoking habits. These will also depend on which neighborhood one lives in. It has been shown that the practice of smoking is favored by the proximity and density of points of sale for tobacco. These are often concentrated in deprived areas. Van Lenthe and Mackenbach have also found that people from deprived communities are more likely to smoke but even more so if they live in stressful neighborhoods. Stressors included "physical quality (decay), required police attention, noise pollution from traffic, and population density in neighborhoods." Similarly, objective and perceived measures of neighborhood crime have also been correlated with smoking.

Smoking also illustrates well the reciprocal and complex relationships among influences. As lower socioeconomic status may incline people to smoke, so better economic and social prospects and the associated better health, increased life expectancy, and security that goes with them provide incentives for quitting smoking or not taking it up in the first place [131].

Other determinants among the broad range of social and environmental influences on smoking include:

- Parents' and peers' smoking are major predictors of youth smoking [132]
- Marketing and advertising—Cigarettes are one of the most heavily marketed consumer products in the United States. According to the American Lung Association [133], the five largest US tobacco companies spent $8.401 billion on marketing in 2018, even with restrictions on electronic, print, and billboard ads. Youth with the greatest exposure to tobacco marketing are more likely to start smoking and to become frequent smokers [134]
- Influence on government regulations through contributions to candidates' campaigns for office [135] and influence on media coverage of the risks of smoking through advertising in major media [136], all driven by the profitability of cigarettes

The many determinants of smoking across multiple levels of influence illustrate well the concept that influences at different ecological levels interact with each other. For example, the genetics of nicotine metabolism and the addictive nature of nicotine create strong markets for cigarettes. Profitability of selling cigarettes drives both (a) enormous advertising and marketing campaigns that promote the anxiety-reducing and mood-elevating benefits of nicotine as well as (b) political contributions to control restrictions on harmful tobacco products. The cycle continues as the success of addicting large numbers of smokers and keeping them addicted ensures the profitability of the cigarette business.

Comprehensive Intervention Programs to Reduce Tobacco Use Smoking rates among adults in the United States have declined from 42% in 1965 to 14.0% in 2019 [137]. This reduction in smoking rate has been achieved through the best example of multilevel population-based health behavior interventions to date. Highlights at the several ecological levels include individualized smoking cessation programs, nicotine replacement therapy, and counseling by health professionals (intrapersonal level), workplace and community-based programs as well as programs tailored to reach different groups (social and cultural level), clean indoor air restrictions (physical environments), news coverage, government reports, anti-smoking campaigns of various health agencies (population-level mass communication), and restricting access to cigarettes and raising taxes on their sale (policy level) [1]. Clearly, interactions among these levels are numerous. For example, clean indoor air policies have driven changes in the physical environment of smoking as well as workplace programs. As another example, the creation of the desire to quit through mass communication and social marketing has cre-

ated markets for the development of improved individual cessation interventions.

There has been considerable development of organizational and community-level interventions to promote nonsmoking. At the organizational level, reductions in smoking have been reported through programs restricting smoking at the workplace [138]. Community-based studies that emphasized community participation in program development have been successful in low-income city neighborhoods and at the county level [139, 140]. COMMIT was a large trial of community organizations designed to improve access to numerous options for smoking cessation throughout entire cities. It achieved appreciable impacts among light and moderate smokers but failed to show benefits among heavy smokers [141, 142]. Commentaries that accompanied the publication of these results noted the importance of broad, public health approaches to reducing population prevalence of smoking [143] as well as ways in which intervention planning might have more broadly and effectively engaged communities, their organizations, and leaders [144].

Extending beyond the organization or community, comprehensive statewide programs have created substantial reductions in smoking. These programs embody broad campaigns of public education, including "counter-marketing" TV advertisements and billboards, increased taxes on cigarettes, support services for cessation, smoking prevention programs for youth, and multicultural approaches, all coordinated through community coalitions [145]. The scope of tobacco policy has expanded to include international initiatives such as the World Health Organization's Tobacco Free Initiative and Framework Convention on Tobacco Control (www.who.org).

Amidst the many contributors to reductions in population smoking, Livingood, Allegrante, and Green have also suggested that mass communication on the harms of cigarettes has had a role to play in this irrefutable "culture change of accommodation to intolerance of smoking" seen in the United States [146]. This is seen to operate through indirect effects through secondary transmission within groups of people rather than being attributed directly to the influence of mass campaigns. This reinforces the message from North Karelia that multilevel and diversity of interventions contribute to bringing about such a change in norms and indeed behavior change.

Finally, the broad ecological approach to smoking cessation is underscored by the recognition that no one type of smoking cessation intervention is reliably effective for 50% or more of those to whom it is delivered [1], and only a small proportion of smokers ever participated in a formal program. Tobacco use is a social and public health problem, not just an individual behavior. Smoking reductions *require* an ecological perspective; population-level changes reflect the aggregate of the many influences promoting nonsmoking, not a single "magic bullet."

Community Organization for Diabetes Prevention in India

The Kerala Diabetes Prevention Program (K-DPP) was a cluster RCT conducted in 60 polling areas of Neyyattinkara sub-district in Trivandrum district, Kerala state in India [147]. Polling areas are well-defined and identifiable locations demarcated with landmarks such as hills, roads, etc. Participants included those at risk according to age, family history, low level of physical activity, and waist circumference as included in the Indian Diabetes Risk Score. The intervention extended over 1 year and included group sessions held on weekends in community settings. After an introductory meeting, two, half-day sessions led by local experts covered key information about prediabetes, diabetes, and ways to prevent it. Trained peer leaders were chosen among group members. They then led meetings to discuss how to apply the information about diabetes prevention to their daily lives. These discussions were held twice in the first month and then monthly for the remainder of the 12-month intervention. Sessions lasted 60–90 min and included 10–23 participants with family members also encouraged to attend.

At the 24-month follow-up, the incidence of diabetes was 17.1% among participants from control polling places who received an educational booklet and advice for lifestyle change, and 14.9% in the intervention polling places (RR = 0.88, $p = 0.36$). The two groups differed significantly, however, in several important areas. Those from the intervention polling places achieved greater reductions in the Indian Diabetes Risk Score ($p = 0.022$). Most notably, incidence among those with impaired glucose tolerance, the primary outcome of the major efficacy studies of diabetes prevention in China [148], Finland [149], and the United States [150], was significantly lower in the intervention than control sites (relative risk = 0.66, $p = 0.03$). Further analyses showed that K-DPP also reduced risks for cardiovascular disease [151]. It was also cost-effective in terms of cases of diabetes-prevented and quality-adjusted life years and from both health system and societal perspectives [152].

The community base of the K-DPP was apparent in an evaluation of its implementation [153]. In addition to the structured sequence of educational and discussion sessions, participants were encouraged to participate in a variety of group activities to support healthy lifestyles and diabetes prevention. These included yoga groups that 31% of participants attended, walking groups—41%, and kitchen gardens—40%. Additionally, the organization of the program at the local, community level of polling places facilitated casual contact between peer leaders and group members. Indeed, 75% of participants reported contact with their peer leaders outside the structured group sessions. Through these contacts, peer leaders provided encouragement for

Table 4.1 Sectors in which actions can be taken to reduce key risk factors for NDCs (reprinted from Fig. 6 in Meiro-Lorenzo et al. [157])[a]

	Tobacco	Poor diet, nutrition	Physical inactivity	Alcohol	Unhealthy environment	Pathogens	Injuries and violence
Health	✓	✓	✓	✓		✓	
Educa-tion	✓	✓	✓	✓		✓	✓
Finance	✓	✓		✓	✓		
Urban Planning			✓	✓	✓		✓
Agri-culture	✓	✓			✓		
Industry	✓	✓		✓	✓		
Transport			✓		✓		✓

[a]Citation: Harrit, Margareta Norris; Meiro-Lorenzo, Montserrat; Villafana, Tonya Luana. *Effective responses to non-communicable diseases: embracing action beyond the health sector (English).* Health, Nutrition and Population (HNP) discussion paper Washington, D.C.: World Bank Group. Document available at: http://documents.worldbank.org/curated/en/698851468325226418/Effective-responses-to-non-communicable-diseases-embracing-action-beyond-the-health-sector. Creative Commons terms of use at: https://creativecommons.org/licenses/by/3.0/igo/

individuals' prevention plans, information about missed sessions, reinforcement of progress, and the opportunity to share and discuss other questions or concerns of participants. Finally, commitment from political leaders in districts and sub-districts facilitated the high uptake of the program.

As with the North Karelia program and the Shanghai diabetes project, K-DPP drew on substantial community input in its implementation. In a low/middle-income country, it then replicated the results of major international efficacy trials, reducing the incidence of diabetes among those with impaired glucose tolerance.

A Policy Strategy: Health in All Policies

To markedly improve population health in an equitable way, it will be necessary to orient policy towards the non-health sector such as housing, and to take into account the environment, especially the built environment, in which people live, work, and play. Social, economic, and cultural conditions should be considered a significant part of our environment. The bulk of evidence from social determinants research and informed practice suggests that in order to improve health and reduce health inequities, it is necessary to act on areas of life and activity lying beyond the health sector [154, 155].

The idea of Health in All Policies (HiAP) is not new. The first article of the Alma Ata declaration proclaims that "…the attainment of the highest possible level of health is a most important worldwide social goal whose realization requires the action of many other social and economic sectors in addition to the health sector." Similarly, the 2010 Adelaide Statement [156] argued strongly for intersectoral action for health. This stressed how cross sector collaboration and joined-up government not only was a key to better health and equity but also may be linked to sustainable development, citizen participation, and more efficient economies. The Adelaide Statement identified a broad range of non-health sector areas and issues: economy and employment, security and justice, education and early life, agriculture and food, infrastructure, planning, and transport, environments and sustainability, housing and community services, land, and culture. As can be easily appreciated, all these areas are related to social determinants of health and tackling inequities. The logical policy follow-up to such initiatives, "Health in All Policies," highlights the necessity for intersectoral initiatives including the health sector.

Table 4.1, from a World Bank report [157], indicates how different sectors such as education, finance, urban planning, agriculture, industry, transport, and health itself may have a significant role to play in reducing risk factors for chronic and noncommunicable diseases.

Healthy Cities

Perhaps the best examples of health in all policies and a "beacon of hope" may be seen in the WHO Healthy Cities movement [158]. Its evolving agenda and philosophy initiated in 1986 incorporate health into urban policy and planning to create healthy, sustainable, and economically prosperous environments and just communities. The Working Cities movement is epitomized by the WHO European Healthy Cities Network, which involves some 100 flagship cities and 31 national networks across the WHO European region [159], This comprises some 1500 cities (some 90 in France alone). Twenty networks have been accredited formally by WHO. These represent 1137 local governments and a population of 156 million people. Healthy Cities endeavor to foster health in all policies by highlighting the importance of improving leadership for health, participatory governance, intersectoral collaboration, and upstream action at the local level to improve population health and tackle health inequities [160]. Different cities and their municipal councils fix priorities and initiate projects in a wide range of environmen-

tal and health domains. In France, these include projects on radon and indoor air pollution, physical and sporting activities to tackle obesity, school transport schemes encouraging walking to school or environmentally friendly vehicles, healthy nutrition, and carrying out a Health Impact Assessment in order to inform decisions about such initiatives. Healthy Cities teaches us that such initiatives need long-term vision and planning. It may take 30 years to reverse the taken-for-granted dependency on cars. Planning may involve thinking, participation, and the implementation of policy changes in successive phases to reach long-term goals [158, 161].

A study of the members of the French Healthy Cities Network investigated how health was taken into account by city authorities through different non-health sectors such as transport, green spaces, social action, youth, education, culture, sport, and housing. Although it featured less strongly within some sectors, e.g., housing policy, health featured prominently in connection with green spaces policy, urban design, and transport and active travel or mobility policy. There is now good evidence that such urban policies prevent disease and impairment, and, important for sustainability, save energy, money, and lives.

City of Well-being: A radical guide to planning [158] provides a wide range of evidence suggesting that "spatial arrangement of towns can influence active travel and recreational activity to a significant extent—and in certain situations it can influence diet" [158]. Walkable, safe environments, and in particular distance from stores and services are key factors in fostering walking and cycling. The fact that this varies substantially from country to country and city to city and neighborhood to neighborhood indicates that urban design taking into account spatial factors and distance can influence norms and reduce dependency on cars. Thus, a joint Canadian and American study [162] cited by Heritage [160] suggests that people living in neighborhoods adapted to walking and in proximity to stores move four times more than those living in areas adapted to cars. However, living in a walkable district or a car-friendly area may not always be a matter of individual choice.

Evidence cited from the United States, China, and India suggests that cycling rather than driving can reduce obesity, diabetes, and hypertension significantly [158]. It is estimated that increasing cycling in the Paris area to 4% of all travel will produce benefits in terms of mortality 20 times greater than the risks due to accidents or accidents caused by cyclists or the effects of air or noise pollution and stress [163].

WHO recently championed a system for assessing the economic impact of changing urban mobility patterns. The Health Economic Assessment Tool (HEAT) which may contribute to broader assessments of health impact allows municipalities to make estimates of the amount of money and lives saved that could be gained through switching from driving to cycling and walking. The value of a statistical life is fixed at 4 million Euros for France, but it is also possible to simply reflect on benefits in terms of the number of lives saved [164]. As an example of such estimates, the French city of Nantes hopes that 12% of all journeys in 2030 will be by bike. If this is achieved, the HEAT calculation shows that 67 lives will be saved each year, or 670 over 10 years. In monetary terms, an estimate is made that 2,682,000,000€ will be saved over the next 10 years if the 12% target is reached. Currently this stands at 4.5% in the Nantes metropolitan area. This in itself represents a saving of some 1,005,000,000€ and 260 lives over 10 years.

In addition to walking and cycling, urban planning may consider the distances needed to walk to stores and services. Other effective policies include car sharing/pooling promoted through strategically placed car pooling parks, transport zoning with 20 and 30 km zones coupled with the designation of cycle lanes, bike parks with credit card renting of both regular and electric bicycles (especially important in hilly cities), chaperoned walking of children to their local school by volunteer parents, signage indicating not distance but the time necessary to walk from one point to another, and general interchangeability in public transport so that transfers from bike, to rail, to bus are cost-free. Coupled with encouraging active mobility, there are also parallel efforts made to render all public places and spaces accessible to physically disabled people using wheelchairs or parents pushing baby carriages, tactile paving guidelines and studs in foot pavement for blind people, traffic signals equipped to give oral cues, and even instructions to blind people guided by personal GPS controllers. If well-planned, cities will not just favor more walking but also chance encounters with people from the neighborhood, thus fostering social support and community ties and benefitting mental health.

Behavior change is not just about education and providing information to individuals but is also about creating new physical, sociocultural, and attitudinal environments which favor healthy behaviors and habits. The healthy cities movement embodies this idea well and illustrates how a holistic view of health and health promotion such as in the following statement of the International Union of Health Promotion and Education that may reap great benefits if applied with intelligence:

> Health is a basic human need. It is fundamental to the successful functioning of individuals and of societies … The main determinants of health are people's cultural, social, economic and environmental living conditions, and the social and personal behaviours that are strongly influenced by those conditions [165].

As much as research may guide and show the value of HiAP and related approaches, evaluation such as through Health Impact Assessment can never be a substitute for political decisions. It will never replace the necessity for politi-

cians to take difficult decisions and have the vision and political will necessary to tackle sources of disease in our environment to develop opportunities for health and well-being, especially where these would seem to run counter to short-term institutional prerogatives or market opportunities [166]. Barton and his co-workers have put forward a Settlement Health Map [158, 167] to explain and analyze the interplay of different factors impacting on health and well-being in the built environment. As Barton suggests this offers a useful tool for generating discussion and debate, thus situating different stakeholders' responsibility within the urban environment, and for shaping intersectoral and multi-stakeholder involvement in creating healthier conditions for urban living [158]. Health Impact Assessment and other evaluation approaches may provide data for consideration in such processes, but they cannot replace them.

Globalization

Globalization and the trends associated with it provide an important context for HiAP. Globalization typically describes changes in production and its organization associated with neoliberalism, the free circulation of information, capital and goods, and the primacy of financial markets over other aspects of the economy [168]. However as Scholte argues [169], it should not be conflated with liberalization as such because other economic policy agendas could be pursued which would highlight the positive benefits of globalization and supraterritorial relations. These are according to Scholte "social connections that substantially transcend territorial geography": [169] a new way of configuring and handling social space. In recent years, such suprateritoriality is epitomized by the Internet and by the fact that local events may become instantly global and have global consequences. This may be seen in communication campaigns such as the response to terrorism "Je suis Charlie" or the current "Me Too" campaign, which denounces sexual violence towards women. Trans-world travel and migration and how business, financial operations, and markets are organized globally working as a network also highlight that we are living in a supraterritorial world. Territorial space can also be bridged, for example, in telemedicine or online trans-world training such as through "massive open online courses" (MOOCs).

Arguably, globalization is not new. There has always been a movement of goods and labor, but distances are being shrunk and travelling times across the world have grown progressively shorter. Current global connections are characterized by transplanetary flows with simultaneity and instantaneity. The premier property of successful modern commerce is its capacity to create universally transferable objects which circulate through frontiers and borders with utmost ease. This aligns well with a neoliberal agenda which espouses the free movement of information, goods, and financial capital, together with the nonintervention of states in the economy and private and business affairs. After some resistance from nonaligned developing countries, this agenda has been taken up by an overwhelming majority of countries in both the developed and developing worlds that now organize or have to organize their economies in conformity with such neo-liberal principles [168]. It is associated with changes in management, work organization, and practices. It has led to the delocalization of industry, reduced wages, and wage costs for multinational companies within a globalized economy.

Geertz [170] has noted that, along with globalization, people living in different communities are also subject to an opposing movement emphasizing the uniqueness of nations, nationalistic ideologies, regions, local products, customs, and beliefs, perhaps as a bulwark against threats to local identities. Thus, people from different countries may not only find similar globalized goods, modes, and beliefs in their countries but also be united by a sense that they must respect their local traditions and ways of doing things. Again, people may strive to be as connected to the contemporary as possible while at the same time falling back on and upholding tradition. Recent political changes may confirm this dialectic and the current move towards political isolationism and a backlash against free trade and political cooperation, e.g., Brexit in the United Kingdom, or the recent emphasis in the United States on "America First." Such apparently contradictory movements (which may be harnessed politically) nevertheless uphold the idea that ultimately, we live in both globalized and localized worlds.

Locality and local cultures should not be opposed to globality and universalism, since both are intermeshed and interact with each other to produce new forms of social organization, space, and sociocultural being. Thus, it is more fruitful in line with the overall socio-ecological model of this chapter to avoid dichotomies and to conceptualize social space as not being made up of discrete entities but incorporating both the global and the local and similarly characterizing the people living in them as having plural identities influenced through both their global and local cultures. Furthermore, it is also wise not to demonize globalization since it also allows the quick transfer of knowledge and experience to enable and emancipate people.

We live in a global world on one planet, and ultimately, we are all affected by planetary factors such as global climate change, migration, widening inequities, the emergence of infectious disease, and noncommunicable disease epidemics. The latter, for instance, are associated with the spread of tobacco and obesity. These however are driven not by globalization as such, but rather by the neo-liberal harnessing of this phenomenon for private profit.

Globalization and Health

Bearing such complexities in mind with respect to different contexts, globalization has been argued to produce both positive and negative impacts on health [171, 172]. In 2001, Feacham claimed that "Globalisation is good for your health, mostly" [173]. Dollar maintained that "the higher growth that accompanies globalization in developing countries generally benefits poor people … globalization has indirect positive effects on nutrition, infant mortality, and other health issues related to income" [171]. Among the negative aspects cited were the spread of disease (AIDS) due to increased migration and travel as well as the impact of tobacco through free trade [171]. Huynen et al. [174] citing Fidler [175] suggest that the World Trade Organisation has more influence on the governance of global health than the WHO and that it is unclear whether World Trade Organization agreements may protect health.

Globalization appears to have affected some countries, such as Asian countries, more positively than others (African, Latin American, and Eastern European countries). On the one hand, slow and uneven growth was associated with stagnation in health indicators, and on the other, economic crises in middle-income countries such as the former Soviet Union produced economic instability, sharp rises in unemployment, and dramatic effects on health and life expectancy. Additional negative claims have included that globalization has had deleterious impacts on health and has worsened health inequities, especially in poor developing countries and among poor households [176–178]. Of particular interest with respect to health and inequity is the observation that "high income inequity reduces the pace of growth and of poverty reduction" [172].

Income Distribution and Other Effects of Globalization

Recent work on austerity shows that recessions can impact people's health not only negatively, as one would intuitively suspect, but also positively [179]. This may largely depend on whether support from social protection systems is maintained or cut. Ironically however recession in itself may have less effect than the austerity measures taken to combat it, measures that arguably are bad for health and kill massively [180].

"Population health tends to be better in societies where income is more equally distributed. Recent evidence suggests that many other social problems, including mental illness, violence, imprisonment, lack of trust, teenage births, obesity, drug abuse, and poor educational performance of schoolchildren, are also more common in more unequal societies" [181]. The measure of inequity taken is how much richer the top 20% are than the bottom 20% in each country. Significantly, in richer countries, what counts is not absolute wealth but whether the wealth is distributed more or less equally. As Wilkinson has stressed [181], it makes little difference how a degree of equality is achieved. Countries such as Sweden and Japan are vastly different in many respects and have different social protection and fiscal systems, but their relatively low degree of income inequity correlates well with health and may be contrasted with the situation in less equal societies. The situation with respect to inequity and health and other social indicators seen between countries is also mirrored among states in the United States with the highest degree of inequity also have high levels of poor social outcomes including health.

Of particular importance is the labor market. Bambra [182] reminds us that "work (paid wage labor) and worklessness (lack of paid work) are not the discrete activities of individuals, but are essential parts of the way in which the totality of society is politically, socially, and economically organized." Being in work is an important condition for health, having an income and for social inclusion, but can also lead to bad health through the impact of an adverse physical or indeed psychosocial working environment. These risks follow a social gradient, with lower-paid workers being more vulnerable to workplace hazards and accidents as well as having less control over their work and related stress in the workplace.

Supranational Policy

One example of the influence of European policy on national policy is the regulatory context of urban planning and environmental health in the European Union (E.U.). The Green Paper and the Leipzig Charter put forward an integrated sustainable urban development to overcome demographic, social, and environmental problems in European cities. Two EU Directives have been implemented to address the issues related to ambient air quality (2008/50/EC) and environmental noise (2002/49/EC). The Parma Declaration (5th Ministerial Conference on Environment and Health in 2010) [183] described the way forward in the work of environment and health in Europe. It set out concrete targets to tackle key urban environmental risk factors, paying special attention to children's health, inequities, and emerging environmental health challenges.

The influence of supranational policy agendas sets the scene for national legislation and implementation and can have both positive and negative effects on health. This can easily be seen in another important non-health field within Europe, namely agriculture and food policy. The Common Agricultural Policy provides a strict regulatory framework and subsidies for farmers in Europe. This has important

impacts on land use, the form of agriculture practiced, its impact on employment and the environment, and the type and price of food available, favoring either health or disease [184]. Thus, on the one hand, subsidizing beef and dairy production favors high saturated fat intake, and on the other hand, the lack of support for fruit and vegetables favors comparatively high prices and lower consumption, all with obvious implications for health. Consequently recommendations have been made for public health policy and agricultural policy goals to be aligned to favor higher and more equitable consumption of fruit and vegetables and less sugar, dairy produce, and meat [184, 185].

Interactions Among Determinants and Sectors

A central point of most writing in these areas is that different environmental or contextual determinants often interact in their influences on health. Good examples include the relationships between air pollution and poverty. Irrespective of the levels of exposure, there is a correlation between being poor and the resultant harmful effects of pollution. This would seem to be related to the second mechanism of differential susceptibility. Through having been exposed to repeated insults of their environment during certain periods of their lives (windows of exposure) [186] poorer populations have developed a greater susceptibility to the resultant health effects. As Deguen and Zmirou conclude, in the case of ambient air quality, long-term multipolar urban planning and diversity-sensitive housing policy may be the best way to tackle environmental and social inequities and to mitigate differential health impacts [187].

Examples: Housing and Urban Life

To further the discussion of HiAP, we will now take a more detailed look at two of the most important non-health sector areas: housing and urban planning and development, and how these impact on people's lives.

National and local government policy with respect to issues such as mortgages, local housing taxes (rates), and rent fixing will largely determine whether the supply of social housing is high or low. Access to social housing (housing owned and rented out by local authorities to people with low incomes or specific needs) will for the most part be determined by residence in the community and recognized needs, such as being a lone woman with children. In France, a country with a tradition of strong social policies, it is estimated that more than 500,000 people do not have a home. Among those, 133,000 are actually homeless; others are living on the sofas of friends, in hostels, squats, etc. [188]. If the number of people living in very "difficult housing" (chronic overpopulation, dangerous buildings, lack of basic amenities) is added, the number rises to 3.6 million, more than 5% of the French population. Another 5 million people are considered to have a very fragile housing situation (lack of house maintenance, large unpaid rents, etc.), and nearly 3.5 million face fuel poverty [188].

Even if appropriate and affordable housing has been heralded as a fundamental human right, it remains one which is far from being upheld in many developing and developed countries alike. The WHO "Closing the gap in a generation" report warns that "One of the biggest challenges facing cities is access to adequate shelter for all. … This crisis (of housing) will worsen social inequities in general and in health in particular" [189]. A 2009 Call to Action from the US Surgeon General asserted that "To improve the nation's overall health, we must improve the health of the nation's homes and ensure that safe, healthy, affordable, accessible, and environmentally friendly homes are available to everyone" [190].

Closely related to housing, indoor air pollution can be caused by both chemical and biological sources. Interventions directed at these can be effective, however. Lead hazard control in the United States has been shown to be a very effective intervention, decreasing dust lead levels by 78% over a 3-year period [191]. In France, exposure to radon is the second leading cause of lung cancer after tobacco, causing up to 2900 deaths per year [192]. Radon mitigation is effective in reducing individuals' risk of lung cancer and is cost-effective compared to other health care and environmental interventions [191].

Examples: Urban Environmental Impacts, Planning and Development

More than half of the human population worldwide now lives in towns and cities. This is likely to increase to 60% by the year 2030. In Europe and the United States, 75% and 80% of people, respectively, live in urban areas [193, 194]. In the developing world, this is likely to lead to megacities in Asia and Africa with 2 billion people living in slum conditions worldwide. Thus, it is important to draw lessons from the healthy cities movement to prepare for an increasingly urban world [195].

From a physical perspective, the urban environment has also assumed considerable importance due to its high population density, the size of buildings, and the existence of a considerable technical infrastructure coupled with diverse industries that have a high potential for different kinds of environmental pollution impacting human health. These may aggregate or intensify the chemical and biological hazards associated with housing described above. Noise provides a good example. An increase of 10 dB in sound intensity is

associated with an increase in prescribed sleeping pills, and cardiovascular disease medications [196].

The Chicago, 1996, and French, 2003 heatwaves illustrate how the urban environment may also exacerbate risks to health. Built-up environments lacking trees, hedges, bushes, and other plants tend to conserve heat (or cold). The impact of such events on mortality and morbidity is exacerbated by vulnerable isolated members of the population being trapped in veritable islands of heat within the urban environment [197].

The design of the neighborhood and the provision of urban green spaces have an impact on health risks by influencing aesthetic perceptions, determining physical constraints, and determining the degree of social mixing. Poorly maintained and deteriorated urban environments are associated with lower levels of physical activity and increased rates of overweight, partly explained through people's perception as a reaction to the aesthetic impression, which also affects mental health and social isolation. The presence of accessible municipal services, public gathering places, and green areas can counteract some of these effects. In addition, environments mimicking natural conditions (green corridors, parks, etc.) help reduce ambient air pollution, cool urban areas, provide a barrier against noise, and may even have an influence on preventing the development of some forms of cancer [198]. A 2020 study found that these considerations include the proximal urban environment. A comparison of the proportion of streets and green spaces within 400 m of homes found that the proportion of streets was associated with overweight or obesity, higher media use, less outdoor activity, and more emotional problems among children and youth, while the proportion of green spaces was associated with more outdoor activity during the winter months [199].

Capabilities go beyond achieving a set goal to encompass the idea that what matters is possessing the freedom to envisage and choose from a range of possibilities in relation to the projects and life plans that people have reason to value. Neighborhoods structure the health practices that people engage in, notably through the unequal distribution of resources. The idea of resources may be widened to include not just physical resources but also intangible resources which may be seen as relational processes. Neighborhoods are not just passive geographical spaces but also living dialectics of structure and agency in which people adapt to constraints and embrace freedoms in different domains over time; they are places where individuals and communities engage in practices producing health on a daily basis [200].

Given that low-income populations are disproportionately found in environments with worse urban features (less green spaces, poor urban design, etc.), many different approaches have been developed in the last decades to address health inequities by changing the neighborhood characteristics of low income people. One approach to changing neighborhood characteristics is to move people from high- to low-poverty neighborhoods. Moving neighborhoods can improve mental health, reduce obesity, and impact positively some wider determinants of health [201]. Several studies have examined the effects of giving people housing vouchers to change homes and neighborhoods. "Moving to Opportunity" permitted families to move from public housing in high-poverty neighborhoods to private housing in lower-poverty or non-poor New York neighborhoods. Moving out of the public housing/high poverty neighborhoods was associated with lower distress among parents and lower anxious/depressive and dependency problems among their sons [202]. Similarly a randomized environmental experimental intervention carried out in Chicago [203] has shown that obesity and diabetes risk may be reduced by moving to different neighborhoods. Three groups were constituted. One group was offered housing vouchers, provided they changed addresses and moved to another neighborhood. Another group was offered the equivalent sum but was given no instructions or advice on moving, and a third, control group was offered neither advice nor money. Over a 7-year period, there was no significant difference between the latter two groups, but the objectively measured risks of developing obesity and diabetes were reduced in the group who moved home. Positive effects were seen 10–15 years later in the prevalence of obesity and diabetes [203].

Evaluation of the effects of moving inhabitants out of unhealthy neighborhoods shows benefits that might be achieved but not a feasible approach for general application. Urban regeneration programs aiming at the whole neighborhood level are argued to be more cost-effective than the movement of individuals to better areas, including because they benefit the community as a whole [204]. Yet the evidence supporting this idea is still weak. A systematic review in the United Kingdom [201] found small positive impacts on socioeconomic determinants of health but potential negative impacts as well. Mixed tenure has also been promoted in many European countries as a means to tackle social exclusion and create sustainable communities. However, the evidence is inconclusive on whether it actually promotes social cohesion, residential sustainability, or improves people's perceptions of the neighborhood. Nor has it been found to provide better job opportunities or changes in income mix [204].

Other interventions that have the potential to improve health and health inequities include: the demolition of distressed housing and relocation of residents; universal design standards to favor the elderly and people with disabilities; crime prevention through environmental design; smart growth and connectivity designs; zoning (regulating how land or a site may be or not used for certain purposes, e.g., prohibiting alcohol outlets near schools); and interventions concerning green space around housing [205].

Urban environments are already home to two-thirds of people with diabetes. This makes cities the front line in the fight against type 2 diabetes. In 2014, three global partners, Novo Nordisk, Steno Diabetes Center Copenhagen, and

University College London, launched the Cities Changing Diabetes (CCD) program to accelerate the global fight against urban diabetes. Today, the program has established partnerships with key stakeholders in 41 cities around the world to address the social, cultural, and environmental factors affecting type 2 diabetes vulnerability among citizens living in the cities [206]. The CCD partners have modeled that it will take a 25% reduction in obesity from 2017 levels to hold the rise in diabetes prevalence at 10.0% globally. This is CCD's long-term global target for 2045. Tingbjerg Changing Diabetes in urban Copenhagen is an example of a long-term strategic engagement which is carried out within the framework of CCD. Tingbjerg Changing Diabetes is a multilevel intervention to promote health and social development while preventing diabetes in urban Copenhagen by using the supersetting approach to mobilize citizens and public, private, civic, and academic stakeholders for collective action across sectors [207].

Although the incidence of type 2 diabetes has not yet declined in the neighborhood, the initiative has, by the end of 2021, managed (1) to establish a strong and dynamic alliance of dedicated stakeholders working with the shared purpose of strengthening community cohesion in Tingbjerg while supporting its residents to adopt healthy lifestyles; (2) to establish vibrant physical settings where residents engage collectively in the social development and health promotion of the community by organizing initiatives such as urban gardening, food and craft workshops, restaurants, and mentor-based support to health systems navigation; (3) to promote participation and engagement in joint activities among residents of all ages, genders, cultural affiliations, and ethnicities; (4) to mobilize and retain socially marginalized residents; (5) to strengthen the commitment of a wide and flexible network of frontline workers to support activities and projects in the neighborhood [208].

Neighborhood Design and Social Isolation

A rapidly emerging area of research that epitomizes the ecological perspective is that regarding the impact of our physical and built environment on our social relationships and behavior. As background, there is ample evidence about the association among mortality, health, and social isolation.

A meta-analysis of 148 studies involving 300,000 persons documented that individuals with strong social relationships had a 50% increased likelihood of survival over an average study period of 7.5 years compared to individuals with weak social relationships [209]. Moroever, associations between social isolation and type 2 diabetes have been documented in several studies [210, 211].

Research suggests that architectural design impacts social isolation and integration. Among older adults in Chicago, Illinois, in the United States, social isolation was more common in dilapidated, run-down areas [212]. In addition, elderly people who lived in high-rise public housing buildings were less likely to venture into neighborhoods than those who lived in low-rise public housing buildings (after controlling for other environmental aspects and personal characteristics) [212].

The complications among the effects of policies are illustrated, for example, by the influence of neighborhood design not necessarily following the influence of neighborhood economic status. In Singapore, almost 90% of residents reside in Housing Development Board public housing, which functions as a neighborhood block in which residents are able to access social support services for the elderly and children along with public spaces such as playgrounds, markets, and cafes [213]. The remaining 10% with higher household incomes reside in private housing. In a cross-sectional study among approximately 4500 Singaporeans over the age of 60 [213], Wu and Chan found that the strongest predictors of lower isolation were residence in housing board public housing and daily social participation in housing board neighborhood events. Accordingly, they hypothesized that the housing board built environment functioned as a community and encouraged social care, social support, and social interaction among residents. In contrast, those who resided in private condominiums or gated communities were at greater risk for social isolation because of less frequent social interaction and lower proximity to others [213].

As the built environment may discourage social interaction, several features have also been linked to increased social interaction. In particular, indoor and outdoor common spaces have been shown to support social ties among older individuals [214]. By offering opportunities for informal face-to-face contact, common spaces allow individuals to foster and maintain casual social relationships that have been found to be associated with health, including among older adults [215]. In a study of older individuals aged 60–90 in Chicago public housing buildings [214], those who lived in the closest proximity to trees and vegetation experienced higher levels of social support and integration than those with little nearby vegetation. Moreover, in a study of 273 Hispanic elders living in East Little Havana in Miami, Florida [216]. researchers found that architectural features such as porches and stoops encouraged greater person-to-person contact and were positively associated with perceived social support and negatively associated with psychological distress.

One might expect that architectural features that make housing pleasant, such as windows, might allow for broader observation of the surrounding area and increase a sense of connection. But in one study, such windows actually removed individuals from close person-to-person contact and resulted in lower levels of perceived social support. Along with the observation from Singapore about the socially isolating effects of private housing for wealthy citizens, this suggests the importance of critical appraisal of environmental, architectural, and urban design. What may seem pleasant or even

luxurious may, in actuality, be isolating or unhealthful. Common spaces that actually encourage individuals to engage with others are necessary to increase social connections and support [216].

In addition to common spaces and architectural design, social interaction may also be influenced by the perceived accessibility of resources. Richard and colleagues [217] conducted a study to assess neighborhood correlates of social participation among older adults living in an urban environment in Montreal, Quebec. They found that a significant predictor of social participation was perceived accessibility to key resources, in that greater access to key resources within a 5-min walk was associated with increased social participation. This has been confirmed by several other studies, which have found that higher levels of participation occur in places where people hold a positive image of their environment [212, 218]. For instance, Bowling and Stafford [218] conducted a cross-sectional study of perceptions of neighborhood infrastructure and social engagement among older adults. They found that perceptions of poor local facilities in the area, particularly poor facilities for people aged 65 and older, were associated with a greater likelihood of low social activities. This suggests that the accessibility of social resources, services, and facilities is an important determinant of social participation and interaction. This emerging field of evidence thus points to an association between the built environment and social support, whereby neighborhood design, architectural features, and perceived accessibility of resources influence individuals' levels of social support and participation. However, research is still needed to document how these components can be manipulated in existing settings to reduce social isolation.

HiAP and Community Organization

It has been argued that HiAP approaches are distinguishable from other intersectoral initiatives to advance health equity in two important ways [219]. First, because they emphasize health in all *policies*, HiAP approaches are coordinated primarily by the formal structures and mechanisms of governments that are responsible for policies. Second, initiatives adopted under HiAP approaches are explicitly linked to structural or long-term governmental policies or agendas, rather than focusing on specific problems. While recognizing the importance of applying the HiAP approach at the governmental level, it has also been argued that intersectoral collaboration and action should also be nurtured at more local levels. The Sundsvall Statement on Supportive Environments for Health, which emerged from the third International Conference on Health Promotion in Sundsvall, Sweden, in 1991, thus recommended the building of alliances and strengthening cooperation between health and environment campaigns and strategies to advance supportive environments at the community level [220]. Health in All *local* Policies is thus a meaningful concept in the context of local community development when referring to the policies and strategies of all stakeholder organizations involved in decision-making and agenda setting, and not just local government institutions [221]. The meta-message of this chapter clearly applies here. Because of the multiple layers and sectors of multiple determinants of health behaviors and health, the broadest possible range and diversity of sectors and influences should be brought into campaigns to address important health problems and challenges. We should reject analyses or rhetorics that privilege one or another approach.

A Key Change in Perspective

Increasing emphasis on non-health policy flies in the face of representations of health that are taken for granted in the general population. Health is often reduced to health care, and this is how governments and citizens traditionally represent health, dividing up the world into health and non-health. Similarly, health is often viewed as determined by individual characteristics—e.g., "good genes"—and individual choices. This may lead to viewing the individual as responsible for her/his own health [222]. In contrast, the ecological perspective casts such views as imposing an unreasonable attribution of responsibility to the individual—a sort of victim blaming—by ignoring the diversity of forces that shape each individual's behavior. Some may see such "robbing" the individual of responsibility as a reduction of individual and human dignity. This concern about dignity may represent a Western view that individual dignity and recognition of external influence are somehow opposed. In other cultures, influence of the environment is assumed and not seen as detracting from the dignity of the individual [223].

A 2015 French study [224] suggests that local stakeholders involved in a community project may perceive health more broadly than might have been anticipated. They were described as seeing health "as a global resource for life, determined by a large number of factors (behaviors, social life, work conditions, education, transportation, etc.), and for which every local actor has a responsibility." Similarly, the success of a Healthy Cities initiative in Portland, in the U.S. state of Oregon, shows that such policies can be acceptable and effective outside of Europe's strong tradition of social and health protection.

The example of Penwerris, in Falmouth, Cornwall, in the United Kingdom, provides a model for changing perspectives and achieving intersectoral collaboration at the community level. In 1995, this socially deprived area had the highest number of poor households, the highest proportion of children in households with no wage earners, and the second highest number of lone parents. More than 50% of homes lacked central heating, and the illness rate was 18% above the

national average [225]. Community health nurses, known as "Health Visitors" pinpointed 20 residents who they felt could work constructively on the estate's problems with the authorities. Five agreed to participate. The health visitors went on to initiate intersectoral action, inviting the representatives of health, social services, education, local government, and the police to a series of meetings. Most importantly, in parallel with an injection of funds following a successful application for an energy improvement grant for the area, a shift in power was granted by the authorities to allow the community partnership to fix priorities and take decisions about their own community and lives. Problems were discussed and "discovered" between the actors, with different solutions being explored. This was not based on classical needs analysis carried out from above, but emerged and relied on local knowledge, ideas, and initiative. Regeneration was not planned from outside but emerged from within [225].

Five years later, the situation had undergone a spectacular and radical transformation. Improvements in a whole series of community indicators had occurred including a 50% drop in crimes, a 42% fall in child protection registrations, and a 70% drop in postnatal depression. Furthermore, there were no unwanted teenage pregnancies, educational achievement had hugely improved, and the unemployment rate had fallen by 71% for both men and women [225]. Interviews and two focus groups to understand the process of change suggested that, in line with complexity theory, the downward spiral of social deprivation and urban decline was reversed through acting at a critical point, developing trust and self-confidence, favoring self-organization within the community, and leading to a reconfiguring of social relationships among residents, different statutory agencies, and new actors. This success has led to similar initiatives with other deprived communities based on similar principles of trust and self-organization being set up in other urban areas in the United Kingdom [226].

Implicit in the emphases on ecological determinants and, especially, Health in All Policies is a focus on general health and well-being, not one or a particular disease. As agricultural policy, for example, will affect diet and all the diseases that nutrition influences, the breadth of impacts on health will be necessary to justify proposals to alter policies not directly related to health. Surely a proposal for major changes in national agricultural policy to benefit a small number of people with a specific disease would have much less likelihood of adoption than one that may be justified as benefitting all children and adults in a society. So too and consistent with considering the many determinants of health, it is important to consider health beyond the prevention of disease and incorporate salutogenesis and resources for health and well-being, favoring a sense of coherence and quality of life [227–229]. Again, the broader focus makes excellent conceptual and policy sense and also recruits additional reasons in support of policy proposals that may emerge from it.

Extension to Diabetes

We have presented a range of ways non-health sector factors and policies may impact human health. We have also sketched a number of different policies that may reduce or mitigate deleterious health impacts. We have also stressed that health should be seen positively and that the physical and sociocultural environment have the potential to promote and improve health. Increasingly non-health policy is taking up the gauntlet and addressing a number of these issues at the macro and micro levels. At the macro level, this has been tackled notably through adapting recommendations from Health in All Policies within national and supranational government policy agendas. At the micro or local level, numerous initiatives tackle proximal lifestyle issues and at the local level the practice of carrying out systematic health impact assessments on new infrastructure development projects. Also, at the community and city level, collaborative community organization such as the supersetting approach has been shown to be effective.

As a way of summarizing the many topics the chapter has addressed, Table 4.2 sets out the advantages or contributions several of the approaches can make towards diabetes prevention and management.

Table 4.2 Examples of application to diabetes prevention and management of multilevel, multi-sectoral interventions

Peer support	A major approach to dissemination of the Diabetes Prevention Program in the United States is group-based, implemented by trained nonprofessionals [230]
	Substantial evidence for the benefits of group, individual, and dyad-based peer support in diabetes management [79]
Community organization	Kerala Diabetes Prevention Program [147]in rural communities in India utilized community engagement in program development and implementation and replicated the results of major diabetes prevention programs [148–150] while reducing CVD risk
Health in All Policies	Urban, agricultural, housing, economic, transportation, and business policies of local, regional, national, and international governments all influence activity levels, diet, stress and emotional well-being, as well as access to care and adherence to preventive and treatment regimens for diabetes and other chronic diseases
Multi-sector, multilevel engagement	The global prevalence and burdens of diabetes in terms of health impacts, complications, quality of life, and costs of care for the disease and its many complications all justify the engagement of all sectors of society and government in prevention and improving its treatment
	Tingbjerg Changing Diabetes is an example of a long-term multilevel engagement to promote health and social development while preventing diabetes in urban Copenhagen, Denmark, by using the supersetting approach to mobilize citizens and public, private, civic, and academic stakeholders for collective action across sectors [207, 208]

Concluding Thoughts

In contrast to old oppositions of nature vs. nurture, genetics vs. environment, or biology vs. psychology, twenty-first century science is clear that causes of health, illness, and well-being are complex, multidimensional, and interactive. Those with serious diseases need good medical care, but it is also clear that economics, policies, environments, organizational and social factors, personality, and a host of other contextual features play major roles in the etiology of health problems, their prevention, and their management. Moreover, despite frequent pessimism as to population trends in health, a broad range of community, health education, and health promotion approaches addressing community, policy, economic, social, and personal factors can be successful in reducing populations' health problems, such as cigarette smoking in the United States [1, 143] or cardiovascular disease in Finland [114, 116, 117].

At least since Villermé's writings of the nineteenth century [231], we have known that the places where we live are not equal as regards health, well-being, and indeed death. Here we have emphasized social, community, and non-health policies over clinical care. In line with Health in All Policies, it will become more and more necessary for government, policy makers, and indeed stakeholders to accept that all these segments have important parts to play in making the world a healthier and safer place. Such a realization however is also linked to our values and views on the sources of inequity and health. It is clear that inequity is a major source of poor health and disease. It is also abundantly clear that the social, community, and non-health sectors could have a substantial role in righting such inequities. In *t*he field of environmental health, a sea change has occurred through the recognition that we all live in the same world with finite resources, and this has opened the way for greater sustainable development and more friendly environmental policy. We believe it will be necessary for a comparable change of representations to occur, accepting that the health and welfare of individuals are deeply tied to the circumstances and environments in which they work, live, and play.

The time has perhaps come when it will become habitual to think of people as being embedded in sociocultural and economic contexts with habitual practices rather than as decontextualized individuals within statistical populations with free choice of behaviors and free choice of dwelling and neighborhood [232]. Once this way of thinking has become normative, then the determining role of the social, community, and non-health sectors and the necessity for different sectors and the health sector itself to work together will be very apparent. Furthermore, the idea that insalubrious, rundown, unhealthy, unsafe, non-accessible, or segregated environments are acceptable will become unthinkable and a thing of the past.

Multiple-Choice Questions

1. Reduction in income, education, and socioeconomic status is associated with:
   (a) Improved health and decreases in mortality and morbidity
   (b) No changes in health, mortality, and morbidity
   (c) Better health and increases in mortality and morbidity
   (d) **Worse health and increases in mortality and morbidity**
   (e) Worse health and decreases in mortality and morbidity
2. Social determinants of health:
   (a) Are irrelevant in the development of health risks
   (b) **Play key roles in the development of health risks**
   (c) Can be corrected with the use of new medications
   (d) Are important, but only secondary to genetic traits
   (e) Are irrelevant in the paths of infectious disease transmission
3. Epimutations refer to:
   (a) **The relationship between rearing and the adult stress response**
   (b) Abnormalities resulting from environmental factors
   (c) Acute changes in DNA methylation
   (d) Prenatal disorders of genetic development
   (e) Major causes of stillbirth
4. Socioeconomic and social factors:
   (a) Are irrelevant to CVD risk
   (b) Probably are related to CVD risk, but it has not been documented
   (c) **Influence the pathways from the serotonin transporter gene to CVD risk**
   (d) Are the leading contributors to CVD risk
   (e) Are not influential on health status at all
5. Resources and supports for self-management that people with diabetes need to manage their disease in daily life include all of the following except:
   (a) Continuity of quality clinical care
   (b) Individualized assessment
   (c) Collaborative goal-setting
   (d) Community resources
   (e) **Access to the latest, most expensive medications**
6. Sustaining diabetes self-management:
   (a) Is secondary to the level of professional expertise of health providers
   (b) **Is a component of key importance in the ecological approach**
   (c) Is not important because interventions studies include follow-up of 1–3 years
   (d) Is based on a 1-week admission to a specialized diabetes center
   (e) Has negative consequences in the physician-patient relationship

7. Diabetes self-management support:
   (a) Is exactly the same as self-management education
   (b) Is exclusively provided by specialists in the medical office
   (c) Is provided by other patients with expertise
   (d) **Is the ability to assist the individual to implement and sustain ongoing behaviors needed to manage their illness**
   (e) Is unnecessary in diabetes management
8. The best predictor of changes in blood glucose control:
   (a) Medical expertise
   (b) Number and cost of medications
   (c) Absolute compliance with the doctor´s orders
   (d) **Length of time over which interventions are maintained by patients**
   (e) Self-monitoring of blood glucose
9. The most important characteristic of type 2 diabetes and self-management:
   (a) **It is "for the rest of your life"**
   (b) It is impossible to achieve
   (c) It has to comply with protocols for randomized controlled trials
   (d) It is feasible for all patients
   (e) It is totally dependent on new technologies
10. Patients rely on peers:
   (a) To learn how to implement care management plans developed with their clinical team
   (b) To gain confidence to implement a plan of action
   (c) To understand what is important and set priorities
   (d) To gain support in coping with the distress chronic diseases often pose.
   (e) **Peer support may contribute in each of the ways noted.**

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Social Determinants of Health and Diabetes Outcomes

5

Hideki Hashimoto

The following section presents a short review of the existing evidence regarding the societal distribution of diabetes morbidity and mortality. In the third section, theoretical frames relevant to explaining the societal distribution of the disease, including the concept of "social determinants of health," are introduced. The section also articulates the negative impact caused by social stigma on people with diabetes that may interfere with effective self-care and treatment of diabetes. The section further describes the important role of professional circles as public advocators to effectively address due policy and social change. The fourth section discusses how the social determinants of diabetes could be translated into policy interventions to countermeasure the disparity in the burden of diabetes across populations. The chapter concludes with some policy and research implications of the social determinants of diabetes.

This chapter focuses mainly on type 2 diabetes mellitus (T2DM), although type 1 diabetes has also been the subject of social disparity in terms of mortality, morbidity, access to high-quality diabetes care, and effective self-care among people with different occupational classes, educational attainment, and income levels [1]. The mechanism through which type 1 diabetes affects people with lower socioeconomic positions more seriously remains open to academic and clinical debate, and whether the mechanism of the disparity is distinct from that of people with T2DM is unclear. Although access to quality health care is suspected to contribute, some have argued that the "opportunity costs" of properly conducting self-care management, in terms of psychological, economic (including time), and social costs, may be higher for those with lower socioeconomic positions, and this likely prohibits them from effectively protecting their own health. We return to this point later in the chapter.

Social Disparity in the Diabetes Burden

A large body of evidence has been accumulated on the unequal distribution of the incidence, comorbidity, and mortality of T2DM among people, depending on income level, occupational class, educational attainment, gender, race/ethnicity, and the economic development stage of the country where they live [2]. Of these factors, socioeconomic position, measured as household income, occupational class, educational attainment, or the combination of these attributes, has been the most widely studied in terms of its association with diabetes outcomes. In general, diabetes incidence, or the population rate of new development of diabetes, is consistently reported to be higher among those with lower socioeconomic positions in developed countries, and limited empirical findings indicate that this is possibly also the case in middle-low-income countries [3].

It is important to note that the association may vary by gender. A study using data from a European cross-country panel survey of the aged population showed no consistent association between diabetes incidence and education among men, but a significant negative association between these variables among women, which remained even after adjusting for body mass index and lifestyle-related behaviors such as physical activity [4]. Another cross-country study of existing cohorts in European countries found a consistently higher diabetes incidence rate in subgroups with lower education for both genders; this effect remained significant but was substantially attenuated by including body mass index in the analytic model [5]. A study using data from the Canadian Community Health Survey also found an education gradient in diabetes incidence that was clearer among women than among men and was partially explained by body mass index [6]. A nationally representative study using the US National Health and Nutrition Examination Survey also showed a stronger relationship between diabetes incidence and education among women than among men [7]. An exceptional result was reported in a recent Chinese population-based survey, which revealed a negative rela-

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tionship between diabetes incidence and education among men, but not among women [8].

Regarding mortality due to diabetes, a US study showed that lower income and lower education were related to higher diabetes-related mortality [9]. In a similar vein, a number of studies in developed countries showed that lower socioeconomic position was related to a higher chance of diabetes-related comorbidities (e.g., retinopathy and nephropathy) [10–12].

Turning to diabetes prevalence, or the proportion of current people with diabetes among the general population, several studies in middle-low-income countries have demonstrated that subpopulations with higher socioeconomic positions have a higher prevalence of diabetes [13, 14], whereas reports from high-income countries have consistently shown that diabetes prevalence is higher among those with lower socioeconomic status [4, 15, 16]. In Ghana, the associations of diabetes prevalence with socioeconomic positions have been found to differ between urban and rural regions [17, 18].

Mixed results for diabetes prevalence by socioeconomic position could be explained by the associations of socioeconomic position with diabetes incidence and mortality varying across regions and countries by level of economic development. Where the higher incidence of diabetes among those in lower socioeconomic positions has been overwhelmed by the higher mortality of diabetes in that stratum, it may lead to a lower diabetes prevalence among those in lower socioeconomic positions. If the disparity in mortality by socioeconomic position is compensated for by better access to diabetes care and the survivorship of patients in lower socioeconomic positions is relatively improved, it may result in a higher prevalence of diabetes among those in lower socioeconomic positions, simply reflecting the higher incidence of the disease among that subpopulation. Clarification of how the different survivorship across socioeconomic positions contributes to the patterns of socioeconomic disparity in the incidence and prevalence of diabetes requires detailed cross-country population-based cohort studies.

Some studies have focused on socioeconomic conditions in early life. A review of ten existing studies indicated that experiencing low socioeconomic conditions during early childhood was related to current diabetes morbidity, though the association varied by gender and conditional adult risk factors (e.g., obesity) [18]. Very few studies showed a protective effect of low childhood socioeconomic position on adult diabetes status [18].

More recently, a United States-based cohort study reported that early socioeconomic position predicted current diabetes (measured as blood glucose and HbA1c), and the association was significantly mediated by current waist circumference, physical activity, and depressive symptoms [19]. Along the same lines, a population-based study in the Netherlands found self-reported economic difficulties during childhood and parental educational attainment to be significantly associated with current diabetes status, although these associations were attenuated after adjustment for current socioeconomic conditions [20]. Taken together, these results imply that early socioeconomic hardship may increase the risk of diabetes-related risk factors in adulthood through life-course trajectories and critical windows during childhood for the later onset of diabetes in adulthood.

Other studies have explored the association between child abuse experiences and diabetes outcomes in adulthood. A study using data from the Canadian Community Health Survey showed that the experience of childhood abuse was related to self-reported diabetes status, and the association was substantially mediated by diabetes risk factors such as obesity and smoking [21]. Similar findings were obtained in the US Nurse Health Study, in which the participants were registered nurses and therefore relatively homogeneous in their current socioeconomic position. Despite the relatively higher and more homogeneous educational attainment of the study participants, adverse experiences during childhood showed a significant impact on diabetes incidence [22].

These observational studies indicate that the development, disease control, and subsequent prognosis of diabetes are highly dependent on the social context in which people are situated throughout their lives.

Supposed Mechanism of Social Disparity in Diabetes

Individual risk factors for diabetes are related to lifestyle behaviors (e.g., obesity and physical activity), and the control of diabetes requires healthy modification of these behaviors. Indeed, observed socioeconomic disparities in diabetes incidence, morbidity, and mortality were substantially explained by socioeconomic differences in lifestyle behaviors—especially obesity [3, 23]. However, this does not yet explain why such differences in lifestyle behaviors by socioeconomic position and gender occur at all, or how they are translated into disparities in the burden of diabetes.

Brown et al. proposed a model to help us comprehend the complex mechanism of diabetes development within a social context. In this model, lifestyle behaviors, access to care, and the process of care are set as proximal causes that link socioeconomic conditions and diabetes outcomes [24]. Brown et al. further advocated the inclusion of an individual's health literacy, psychological stress, demands competing with self-care activities (e.g., time constraints), and availability of social support as mediating factors linking socioeconomic conditions to lifestyle behavioral choices and effective negotiation with health care professionals for diabetes care. In addition, environmental factors such as the local availability of healthy food, walkability, and safety may also influence whether people

make healthier behavioral choices. However, the most recent review on T2DM and environmental risk factors [25] and other related review articles on obesity [26] and nutrition [27] concluded that, although the built environment (e.g., food access and walkability) is potentially associated with the chance of having diabetes and related risk factors, the strength of the evidence is currently limited because of heterogeneity in measurement and study design, which needs to be addressed by more rigorous research on this important theme.

As described earlier in this chapter, several studies have indicated that socioeconomic conditions affect the access to and the process quality of diabetes care [10–12]. Notably, the majority of these reports have come from countries with universal public health insurance coverage, suggesting that universal health insurance coverage may not be enough to close the socioeconomic gap in diabetes outcomes. Indeed, a study using the United Kingdom-based cohort of the Whitehall II study found that universal health insurance coverage may not be enough [23]. Among civil servants in the United Kingdom, the study found that the socioeconomic gradients in diabetes-related morbidity and mortality were substantially mediated by cardiovascular risk factors such as blood pressure and smoking. Most striking was the finding that such socioeconomic gradients in diabetes outcomes were found even among civil servants, who had relatively good job security, and even in the United Kingdom, where public health care is widely available without an out-of-pocket co-payment.

Social relationships in the family and community are powerful structures that influence the distribution of obesity in society [28]. Social networks are supposed to provide norms about obesity, psychological support, conflict-influencing behaviors, and/or social selection processes where "birds of a feather flock together" [29].

Recent studies have further focused on the social influence of the stigma faced by people with diabetes [29–33]. People living with diabetes are often stereotyped as lazy and undisciplined, and they are blamed for their own diabetes condition. Prevailing social stigma, even among health care professionals, causes psychological and social isolation and excludes people with diabetes from social participation and effective self-care management. Given the seriousness of health care professionals' influence on social stigma, the position statement by Diabetes Australia and the subsequent guidance issued by the National Health Service England advocate that health care professionals should ensure proper use of their words during interactions with people with diabetes [34, 35].

Culture is another aspect of the social context that hinders effective communication and shared decision-making between people with diabetes and health care professionals. Although studies focusing specifically on cultural aspects of people with diabetes are scarce, the existing literature suggests that cultural norms about the body, food, and physical activity influence people's lifestyle-related choices [24].

In addition to macro-social mechanisms, biological mechanisms also need to be understood to see the whole picture of how social context gets "under the skin." The most influential biological mechanism may be the intrauterine programming and thrifty phenotype hypothesis (also known as the Barker Hypothesis) [36]. This hypothesis views exposure to low nutrient intake during the fetal stage as causing adaptation for survival, which, in turn, causes diabetes in adulthood when the nutritional environment becomes richer. Several epidemiological studies have supported this idea because those who experienced poor nutrition during early life had higher risks of obesity, insulin resistance, and diabetes [37–39]. Recent epigenetic research has further investigated how the early environment becomes inscribed on the epigenome as "metabolic memory" that reveals itself later in life as metabolic dysfunction [40].

Another series of studies has suggested the possible role of chronic inflammation. A United Kingdom-based longitudinal survey revealed that about 50% of the excess risk of T2DM incidence associated with a low socioeconomic position was explained by lifestyle behaviors, whereas a quarter of this excess risk was explained by chronic inflammation markers such as C-reactive protein and interleukin-6 [41, 42]. The role of chronic inflammation may indicate a biological mechanism that translates social stress related to low socioeconomic position into a pathological path leading to insulin resistance and beta cell dysfunction.

As described in our review thus far, no single theory can tell the whole story about how social context gets "under the skin" and results in differential diabetes outcomes. This is why two larger frameworks are needed to comprehend diabetes as a social challenge—namely, the ecological perspective and the life-course perspective.

The ecological perspective regards individuals as nested within families, which are further nested within communities, which are further nested within larger social contexts, such as states (Fig. 5.1) [43]. All of these levels (individual, family, community, society) interact with each other. For example, an individual's behavioral choices may be enhanced if he/she has a supportive relationship with his/her family

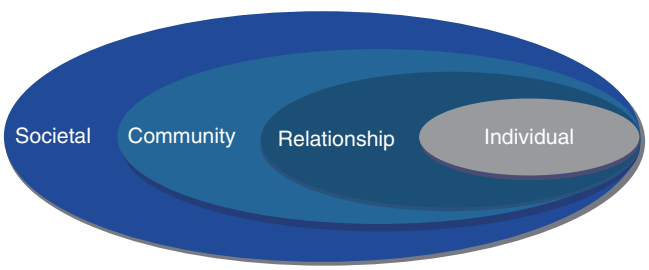

Fig. 5.1 Ecological structure. (Source: Centers for Disease Control and Prevention. The Social-ecological Model: A Framework for Prevention. Downloaded on 15 June 2018 from https://www.cdc.gov/violenceprevention/overview/social-ecologicalmodel.html)

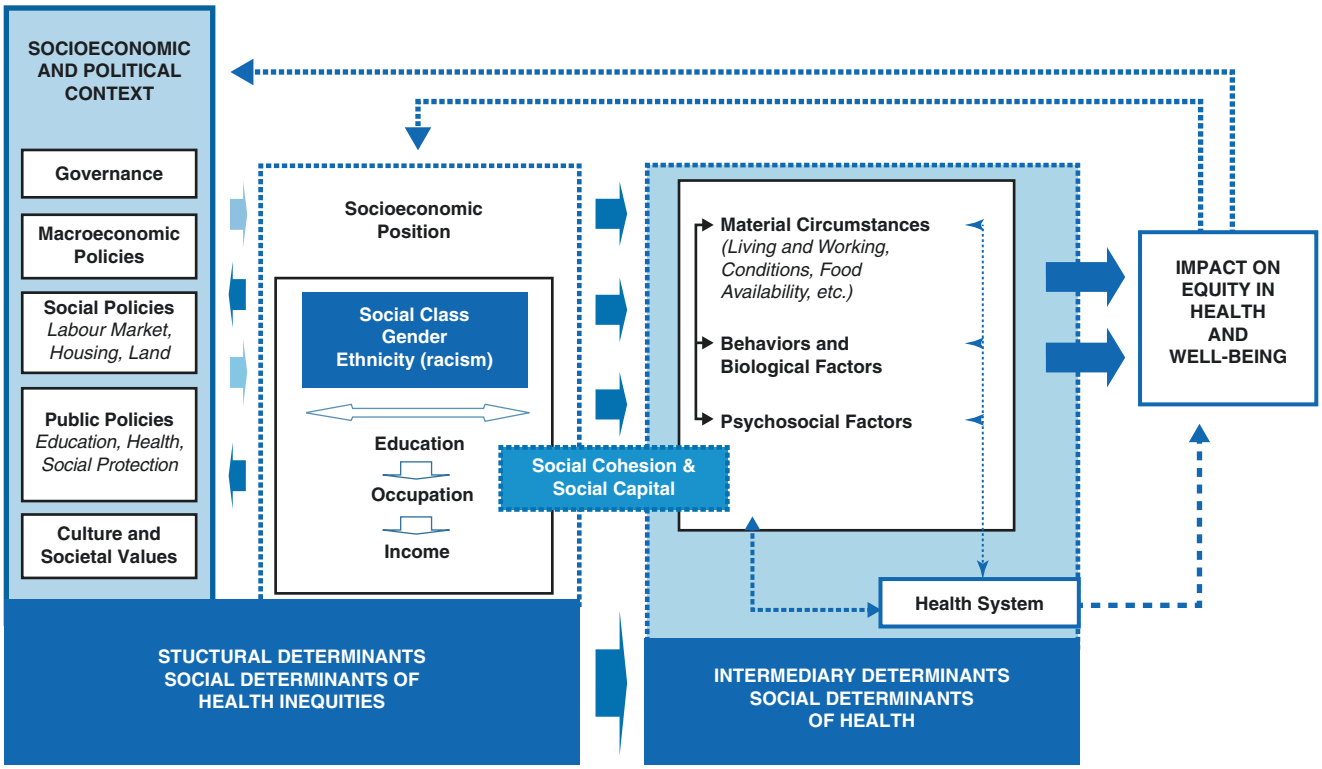

Fig. 5.2 Structural and intermediary social determinants of health and health impact. (Source: World Health Organization (2010) [45]. Conceptual Framework of Social Determinants of Health, Paper 2, Fig. A, p. 6)

and community. A supportive relationship is more likely to be available if the community environment is safe and has relatively less deprivation—factors that will be further determined by a nation's economy and social policies.

The life-course perspective examines the sequence of life stages from the fetal period to childhood, adolescence, young adulthood, midlife, and later stages of life. Each stage exhibits a unique window with specific vulnerabilities to biological, behavioral, and psychosocial risk factors for chronic diseases, and the impact of a certain stage will echo in the later stages [44]. For example, life difficulties in the early stages affect an individual's chances of getting diabetes in later life through biological programming, reduced opportunities to nurture health literacy, and smaller chances of obtaining a secure job and income, which will further impede access to necessary health care resources.

Bridging the ecological and life-course perspectives is the concept of "social determinants of health." This concept sees health as determined not only by medical systems but also by daily life conditions where people are born, live, learn, and work [45]. The concept of the social determinants of health can be applied to diabetes [46]. As the above review shows, to achieve equity in diabetes outcomes, it is important—but not sufficient—to provide equal access to quality health care. The social determinants of health concept indicate that changes should be made in the root causes of the biological, behavioral, psychosocial, and socioeconomic causes of health gaps (Figs. 5.2 and 5.3 [45]). For this purpose, the social determinants of health concept require interventions that are multilevel, multidomain, and longitudinal.

Health care sectors are important, but are not the only institutions that can enable a reduction in health gaps. For example, a study from Scotland based on a nationwide clinical database reported that diabetes incidence declined from 2004 to 2013 in all socioeconomic strata except for the lowest decile—the most deprived group. This group showed a resurgence in diabetes incidence beginning in 2010, after the global economic shock, resulting in a widening socioeconomic disparity in diabetes incidence, especially among women [47]. Apparently, macroeconomic policy is a strong social structural determinant of health. Attention to the social determinants of health calls for inter-sectorial collaboration across health, finance, labor and industry, education, civil engineering, and other sectors in government and global institutions [45, 46].

It should be noted, however, that a recent conceptual review on social determinants of diabetes criticized the existing literature on socioeconomic conditions and diabetes outcomes for focusing too much on individual-level factors, such as behaviors and literacy, and emphasized the significance of the larger social context, such as the health care system and the legal and social policy frames that shape an

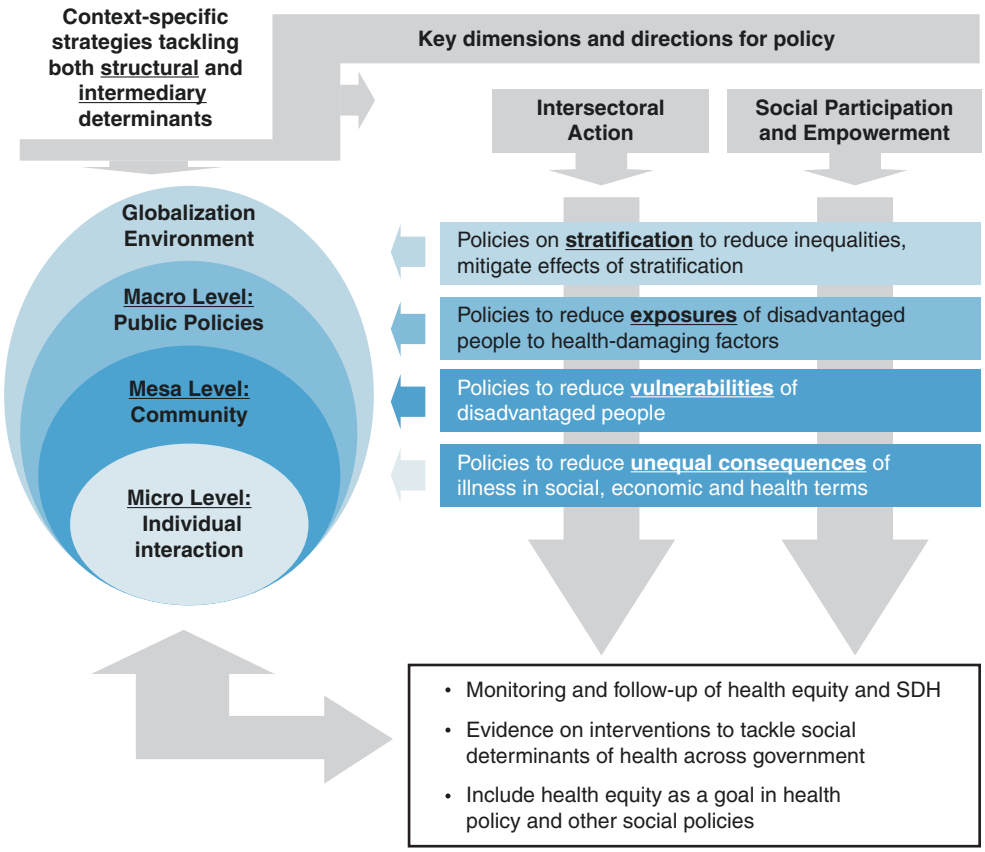

Fig. 5.3 Levels of policy to address social determinants of health. (Source: World Health Organization (2010) [45]. Conceptual Framework of Social Determinants of Health, Paper 2, Fig. B, p. 8)

individual's likelihood of engaging in diabetes-related risk behaviors [46, 48].

This notion logically indicates the importance of social change through policy advocacy, as well as the impact of health educational intervention and psychosocial support for individuals with diabetes. The International Diabetes Federation and other organizations have been leading the advocacy to influence policy, both domestic and international, to improve health care and social conditions for people with diabetes and enable them to exercise better control over their lives [49]. Although the importance of advocacy activities has gradually begun to be recognized among health care professionals, it remains challenging and controversial whether social and political activities should be added to the traditional physicians' code of "scientific neutrality" [50].

Social Determinants of Diabetes Interventions to Close the Social Gap in Diabetes Outcomes

What can be done to close the social gap in diabetes outcomes? A good quality of diabetes care should be available to all people, regardless of socioeconomic status, ethnicity/race, or gender. The introduction of universal health coverage is a high-priority policy for closing the gap [51, 52]. However, this is not sufficient; quality care availability may help to close the gap in diabetes mortality, but it will do little to prevent the gap in diabetes morbidity and, especially, incidence.

Lifestyle and related behaviors are strong risk factors for diabetes outcomes, and the provision of information through community education to support people in making healthier choices is promising. Indeed, a large randomized clinical trial showed that intensive health education can have a significant preventive impact on diabetes incidence if the intervention is properly prepared [53]. However, a longer follow-up of the same randomized clinical trial revealed that the difference originally observed between the treatment and control groups gradually declined over time [54]. This decline was not simply because the program's effectiveness attenuated over time after the intervention ended; rather, it was because behavioral change among the control group patients caught up with that of the treatment group patients over time, suggesting that factors other than the educational program influenced behaviors among patients with prediabetes afterward. Social changes in the norms about healthy diet and habitual exercise, improvements in access to supportive information, and environments facilitating the maintenance of behavioral modifications are the suspected explanations. This supports the idea that behavioral choices are not completely volitional; instead, behaviors are influenced by social,

economic, cultural, and other structures. Creating supportive environments for behavioral modification toward healthier lifestyles is promising. However, existing reviews on the effectiveness of policy interventions such as the development of walkable cities and improving access to healthier food in the community concluded that the current evidence is mixed, and further research on the effectiveness of environmental architecture and other interventions on the social determinants of diabetes is required [25, 26, 48].

Among the possible policy interventions, accumulating evidence has begun to show that a sugar tax, or the taxation of sugar-sweetened beverages, is a promising policy for obesity prevention [55]. The sugar tax and the subsequent price increase of sugar-sweetened beverages are expected to provide disincentives for consumers' purchasing decisions. By nature, this intervention is expectedly regressive: the disincentives have a stronger influence on the poor, who have lower income, suggesting that the impact of the sugar tax on obesity prevention should be largest among the poor, who are also at higher risk of obesity.

Currently, the policy has already been introduced in several countries, including Mexico, where the consumption of sugar-sweetened beverages has been considered a major target for reducing caloric intake for obesity prevention, especially among children and poor adults. In April 2014, the Mexican government enacted a policy to incur a 1 peso-per-liter excise tax on all sugar-sweetened beverages. This has resulted in a reduction in the consumption of sugar-sweetened beverages, and, as expected, the impact was observed to be larger among low-income households and those in rural regions than among high-income households and those in urban locations [56–59].

Although the Mexican policy seems to have achieved early success, the introduction of taxes for health promotion is not simply effective. Recent assessments found that weight reduction was observed only among girls in rural areas, and those with obesity at baseline, while no reduction was visible among boys [60]. Another study found that the reduction in sugar-sweetened beverages was accompanied by substitutional increases in cholesterol and saturated fat intakes, resulting in no change in calorie intake [61]. These recent observations indicate that such a "sin tax" for health promotion should be accompanied by alternative healthy choices at affordable prices for the vulnerable population. Furthermore, the implementation of the sugar tax was challenged by business sectors and lobbying parties with vested interests and was under threat for political feasibility [62–64].

Despite its challenges, the sugar tax can be taken as a good example of the "proportional universalism" approach, or the universal inclusion of people in health promotion, with resource allocation proportional to needs or risks [65]. Because people with diabetes are vulnerable to social stigma, high-risk approaches that target people with high diabetes risks (e.g., targeted educational interventions for patients with prediabetes) often induce discrimination and subsequent social exclusion among targeted vulnerable people. Instead, universalism approaches can provide a wider range of community members with the opportunity for self-management of their own health without selection. In addition to offering community campaigns to reduce social stigma by providing precise information on the etiology and control of diabetes, health care professionals should be aware of the significance of structural interventions for changing the social environment, and take active roles to help people achieve healthier lifestyles in a socially inclusive manner.

Conclusion

Epidemiological and clinical studies have convincingly demonstrated that the disease burden of diabetes is disproportionally distributed across society because the incidence, mortality, and morbidity of diabetes are influenced by the socioeconomic and environmental determinants of diabetes. Lifestyle behaviors such as diet and exercise are significant factors in diabetes control, and they are shaped not only by individual capacity but also by the social environment surrounding individuals. Interventions to improve diabetes control among selective high-risk groups through lifestyle modification have been shown to be effective. However, this selective approach may run the risk of inducing social stigma toward people with high diabetes risk, which may seriously hinder effective self-care. As an alternative, structural interventions to change the social environmental determinants of diabetes are promising, although they require further research and policy evaluation to effectively translate the concept into actions that help people to overcome the social challenges of diabetes. Furthermore, health care professionals specialized in diabetes care should take on more active roles to help people with diabetes overcome the challenges of the disease through improvements in policy and social environments.

Multiple-Choice Questions

1. Which of the following statements best fits the concept of the social determinants of diabetes? (Choose one that fits best.)
   (a) Patients' rights to quality diabetes care should be addressed.
   (b) Patients are responsible for modifying their lifestyles to improve diabetes control.
   (c) The government health sector should provide community education to improve knowledge about diabetes risks.
   (d) **All social, economic, and health policies related to people's life-course experiences should be consid-**

ered in terms of their potential leverage to close the gap in the diabetes burden among people.

(e) None of the above.

2. What determines the prevalence of diabetes? (Choose one).
   (a) Genomic predisposition.
   (b) Local availability of healthy food.
   (c) Education.
   (d) Motorization (transportation by car driving).
   (e) **All of the above.**
3. Which subpopulation is susceptible to a higher diabetes prevalence? (Choose one).
   (a) Richer men.
   (b) Poorer men.
   (c) Richer women.
   (d) Poorer women.
   (e) **It depends on the local stage of economic and social development.**
4. Which of the following options describes a policy intervention that is in the frame of the social determinants of diabetes? (Choose all correct responses.)
   (a) Research and development of genetic treatments for diabetes.
   (b) Patient education to improve adherence to diabetes care regimens.
   (c) **Introduction of a sugar tax.**
   (d) **Improvement of health literacy among community dwellers.**
   (e) **Civil engineering to design a walkable city.**
5. Why is the incidence of diabetes higher among people with lower socioeconomic status in low-middle-income countries as well as in high-income countries? (Choose all correct responses).
   (a) **Limited availability of healthy food.**
   (b) **Limited affordability of resources to sustain healthy lifestyles.**
   (c) **Lower health literacy to support healthy lifestyles.**
   (d) **Early life experience with deprivation and related physical manifestations.**
   (e) **Social influence of close peers with poor diets and prevalent smoking.**
6. Which of the following statements fits the ecological model of health and diabetes? (Choose one).
   (a) An individual's dietary habits are influenced by family and close friends.
   (b) Walking habits are facilitated if the community is safe and walkable.
   (c) Healthy diets are discouraged if the availability of fresh vegetables is limited in the community.
   (d) The national economy affects an individual's chances of having suitable resources to protect their own health.
   (e) **All of the above**.
7. How does the social stigma of people with diabetes affect their self-management of the disease? (Choose one).
   (a) Social stigma blames people with diabetes, considering them responsible for their own disease.
   (b) Social stigma socially excludes people with diabetes from necessary social support.
   (c) Social stigma discourages self-esteem and self-efficacy related to self-management among people with diabetes.
   (d) People with diabetes are forced to conceal their diabetes status in public out of fear of stigmatization.
   (e) **All of the above**.
8. Which of the following options best fits the concept of the "proportionate universalism" approach to tackling social disparity in the diabetes burden? (Choose one).
   (a) Screening for obesity to provide publicly subsidized education programs for behavioral modification.
   (b) Targeting people with low incomes or low educational attainment to provide free vouchers for fresh and healthy food.
   (c) **Introduction of a sugar tax on sweetened beverages to reduce sugar intake in the general population.**
   (d) Free provision of diabetes care for people living in targeted communities, with means testing.
   (e) All of the above.
9. What are the strengths and weaknesses of the population approach compared with the high-risk approach? (Discuss).

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Part II

Diagnosis, Classification and Mechanisms of Disease

6 Definition, Diagnostic Criteria, Screening, Diagnosis, and Classification of Diabetes and Categories of Glucose Intolerance: An Update

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Abbreviations

AACC	American Association of Clinical Chemistry
ABCC8	ATP-binding cassette, subfamily C, member 8
ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DM	Diabetes mellitus
FCPD	Fibrocalculous pancreatic diabetes
FPG	Fasting plasma glucose
GAD	Glutamic acid decarboxylase
GCT	Glucose challenge test
GDM	Gestational diabetes mellitus
GLUT	Glucose transporter
HAPO	Hyperglycemia and pregnancy outcome
HbA1C	Hemoglobin A1c
IA-2	Islet antigen 2
IADPSG	International Association of Diabetes and Pregnancy Study Groups
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
KCNJ11	Potassium inwardly rectifying channel, subfamily J, member 11
MODY	Maturity-onset diabetes of the young
NDDG	National Diabetes Data Group
NGSP	National Glycohemoglobin Standardization Program
NICE	National Institute for Health and Care Excellence
NODAT	New-onset diabetes after transplantation
OGTT	Oral glucose tolerance test
PDAC	Pancreatic ductal adenocarcinoma
PG	Plasma glucose
SSA	Somatostatin agonists
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organization
ZnT8	Zinc transporter 8

Objectives

- The aim of this chapter is to delineate the definition of diabetes mellitus and its diagnostic criteria. Following a brief discussion on the evolution of the current diagnostic criteria, the recent ADA criteria and recommendations for screening will be discussed.
- The section on the diagnostic criteria for gestational diabetes compares and contrasts the various criteria recommended by different professional bodies and their merits. This section will also discuss the utility and fallacies of HbA1C as a measure of glycemic status.
- The section on the classification of diabetes lists the various etiologies of diabetes mellitus based on the pathophysiology or common mechanisms for better understanding. Few subsections like "endocrinopathies" and "drugs causing diabetes" are discussed in brief.

Definition

The word diabetes is derived from its Greek root, which means "to pass through," referring to polyuria—the hallmark symptom of diabetes mellitus (DM). The word mellitus means "from honey," denoting glycosuria, differentiating it from its close mimic, diabetes insipidus [1].

DM is defined by the World Health Organization (WHO) as a metabolic syndrome characterized by chronic hyperglycemia resulting from any of the several conditions

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that cause defective insulin secretion and/or action. Prediabetes is a state characterized by metabolic abnormalities that increase the risk of developing DM and its complications.

Diagnostic Criteria

The diagnostic criterion for DM has undergone a sea change over the last several decades with improved understanding of its pathophysiology and complications. Though the association between chronic hyperglycemia and its complications is well established, the specific cutoff points for diagnosing DM still remain a matter of intense debate.

The WHO, in the year 1965, published the first guidelines for diagnosing DM [2]. The National Diabetes Data Group (NDDG) proposed a criterion based on the observation of the bimodal distribution of plasma glucose (PG) in Pima Indians and Nauruan populations and the risk of progression to DM and the development of complications. The NDDG also recognized an intermediate group of individuals with raised PG above normal, but not satisfying the criterion for diagnosing DM. This group faced a risk of progression to DM at a rate of 1–5% annually and also had higher prevalence of atherosclerotic disease. The terminology "impaired glucose tolerance (IGT)" was introduced to identify this important group of persons in whom early intervention could avert DM and its complications [3].

The subsequent modifications of the diagnostic criteria by WHO saw a revision of the fasting and 2-h post glucose load venous PG thresholds to 7.8 mmol/L and 11.1 mmol/L, respectively, based on the observations that complications of DM rarely occurred below these PG levels.

In 2003, the American Diabetes Association (ADA) made a controversial change to its existing guideline by reducing the cutoff point for defining the upper limit of fasting plasma glucose (FPG). This modification was based on data from four population-based epidemiological studies which showed that the ideal FPG cutoff point fell between 5.22 and 5.72 mmol/L and the cutoff of 5.55 mmol/L was arbitrarily chosen [4].

Glycated hemoglobin (HbA1c) was included as a modality to diagnose DM by the ADA in 2010 and the WHO in 2011.

The latest ADA criteria for diagnosing DM are given below: in asymptomatic individuals, these tests need to be repeated on another day for the confirmation of the diagnosis [5].

- FPG ≥7.0 mmol/L. Fasting is defined as no caloric intake for at least 8 h.
- or
- 2-h PG ≥11.1 mmol/L during an oral glucose tolerance test (OGTT). The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.
- or
- HbA1c ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.
- or
- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random PG ≥11.1 mmol/L.

ADA Criteria for Diagnosis of Prediabetes

In addition to fasting and post-glucose load PG levels, HbA1c is also recommended as a screening test for prediabetes.

The cutoff points recommended for the diagnosis of prediabetes are given below:

1. FPG—5.6–6.9 mmol/L [impaired fasting glucose (IFG)]
2. 2-h PG in the 75-g OGTT—(7.8–11.0 mmol/L) (IGT)
3. HbA1c 5.7% (39 mmol/mol)

It should be noted that WHO defines the IFG cutoff at 6.1 mmol/L.

Criteria for Screening for Diabetes or Prediabetes in Asymptomatic Adults

The ADA 2017 guidelines have laid down certain risk factors for screening for diabetes and prediabetes. These include:

1. Overweight or obese (body mass index (BMI) ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) adults who have one or more of the following risk factors:
   (a) First-degree relative with diabetes
   (b) High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)History of cardiovascular disease
   (c) Hypertension (≥140/90 mmHg or on therapy for hypertension)
   (d) High-density lipoprotein cholesterol level ˂0.90 mmol/L and/or a triglyceride level ≥2.82 mmol/L

(e) Women with polycystic ovary syndrome
(f) Physical inactivity
(g) Other clinical conditions associated with insulin resistance, e.g., severe obesity and acanthosis nigricans

2. HbA1c ≥5.7% (39 mmol/mol), IGT, or IFG on previous testing.
3. Women who were diagnosed with gestational diabetes mellitus (GDM).
4. HIV
5. For all patients, testing should begin at age 45.
6. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status.

Screening for Prediabetes and Diabetes

Prediabetes is an intermediate state of hyperglycemia characterized by elevated PG levels above normal but not qualifying for the diagnosis of DM. Its significance lies in the fact that 5–10% of patients can progress to develop DM annually without intervention [6, 7]. The dreaded complications of DM are also observed in this group of patients, stressing the need for early recognition and reversal of this state.

According to the WHO, prediabetes constitutes two distinct entities, namely, IFG and IGT. Different pathogenic mechanisms are believed to underlie these two distinct entities, and persons with a combination of both abnormalities have more advanced metabolic abnormalities than those with either of the two. Similar to the increasing prevalence of DM globally, the prevalence of prediabetes is also expected to rise, with an estimated 472 million people expected to be affected by this condition by the year 2030 [8]. Although a significant proportion of people progress to develop DM, several remain static, and many go on to revert to a normal state, although the rate of conversion has been reported to be different in various studies [7, 9].

It is well recognized that beta cell dysfunction and insulin resistance are already present in patients at the time of detection of prediabetes [10, 11]. It thus represents a phase in the continuum of worsening beta cell dysfunction and insulin resistance. Insulin resistance is a feature of both IFG and IGT, though the site of resistance varies. IFG is characterized by hepatic insulin resistance, while in IGT, resistance is mainly at the level of skeletal muscles. The beta cell dysfunction is however seen in both [10, 12]. This difference in the pathophysiology is reflected in the PG changes following a glucose load with persons with IFG demonstrating impaired early response in contrast to those with IGT who show impairment of both early and late phases of insulin secretion [12–14].

The ADA recommends screening for DM and prediabetes in asymptomatic people, including those who are obese or overweight and have one or more additional risk factors as listed above. For all others, testing should begin at 45 years of age, and repeat testing in those with normal results is to be done at a minimum interval of 3–5 years [5].

Diagnostic Methods

Glycated Hemoglobin

With sustained exposure to hyperglycemia, proteins undergo nonenzymatic glycation. Hemoglobin A (HbA), the predominant fraction of hemoglobin in normal adults, also undergoes a similar modification. Three minor fractions of glycosylated hemoglobin are known to occur, namely, HbA1a, HbA1b, and HbA1c, based on their elution properties during electrophoresis. The HbA1c fraction that has been widely employed as a diagnostic test has a hexose moiety attached covalently to the NH_2-terminal valine residue of the β-chain of HbA [15]. Several methods have been used to separate this fraction from the nonglycated hemoglobin. These techniques exploit the differences in structure (affinity chromatography and immunoassay), charge (ion-exchange chromatography, high-performance liquid chromatography [HPLC] electrophoresis, and isoelectric focusing), or chemical nature (photometry and spectrophotometry) of the various fractions. HbA1c is a measure of average plasma glucose levels over the preceding 3 months [16]. There are several advantages to measuring HbA1c over plasma glucose. HbA1c estimation can be done regardless of the time of day or fasting status. It also shows less day-to-day variability and analytical stability [17]. HbA1c also predicts the development of micro- and macro-vascular complications of DM, as observed in clinical trials like the DCCT and the United Kingdom Prospective Diabetes Study (UKPDS). However, it is not free from limitations and can be influenced by other non-glycemic factors (Table 6.1). Diseases affecting the red blood cell turnover rate can result in imprecise values. Compared with FPG and $HbA1_C$, the 2-h PG value diagnoses more people with prediabetes and diabetes.

Table 6.1 Factors affecting HbA1c estimation

	Change expected
Physiological characters	
Age	HbA_{1c} increases by approximately 0.1% with every 10 years of age—not relevant clinically
Race	Variably reported
Hematological conditions	
Iron deficiency anemia [18, 19]	Falsely elevated in most studies Mechanism—not clear
Hemolytic anemia	Falsely low due to the shortened life span of RBCs
Hemoglobin variants (HbF, HbS, HbD, HbE) [20]	Variable based on assay methodology
Analytical interference	
Hyperbilirubinemia	Variably reported interference [20, 21]
Hypertriglyceridemia [20]	Falsely low
Others	
Malaria	Falsely low [22]
Transfusions [23]	Falsely low
Splenectomy	Increases life span of RBC in conditions like hereditary spherocytosis, resulting in elevated HbA1c after splenectomy [24]
Renal failure	Falsely low due to shortened erythrocyte life span, frequent blood transfusions, erythropoietin-promoted erythrocytosis, and drug-induced anemia [25]
Alcohol abuse	Falsely low [26]
Aspirin [27]	Modest increase—not clinically relevant

Standardization of HbA1c

The clinical utility of HbA1c largely hinges on the quality of the analytical method used. A plethora of tests are available today for estimating HbA1c. In order to establish uniformity in testing, reporting, and interpreting the HbA1c results, the American Association of Clinical Chemistry (AACC) and the NGSP (National Glycohemoglobin Standardization Program) developed a protocol to standardize the HbA1c test results to those of the DCCT [28].

In 1995, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) sought to establish a true reference method for HbA1c estimation instead of standardizing it to a comparison method like the NGSP. Here, hemoglobin is digested using enzymes that cleave a hexapeptide off the amino terminal of the β-chain. The glycated and non-glycated hexapeptide components are then separated and quantified. HbA1c was calculated as the ratio of two fractions and reported as a percentage [29]. This method is expensive and laborious, making it unsuitable for routine analysis of samples.

Classification of Diabetes Mellitus

It is prudent to try and classify the type of DM in order to identify the best management plan, screen for associated complications and comorbidities, and also screen other members of the family. However, this may not be straightforward in all scenarios. DM can be classified based on the underlying pathogenic mechanisms into the following categories: type 1 DM, type 2 DM, GDM, and secondary DM (Table 6.2) [5, 30].

Table 6.2 Secondary causes of diabetes mellitus

A. Genetic defects of β-cell function
Maturity-onset diabetes of the young (MODY) 3 (HNF-1α)
MODY 1 (HNF-4α)
MODY 2 (glucokinase)
Other rarer forms of MODY
Transient neonatal diabetes
Permanent neonatal diabetes
Mitochondrial DNA
B. Genetic defects in insulin action
Type A insulin resistance
Leprechaunism
Rabson-Mendenhall syndrome
Lipoatrophic diabetes
C. Diseases of the exocrine pancreas
Pancreatitis
Pancreatectomy
Neoplasia
Cystic fibrosis
Hemochromatosis
Fibrocalculous pancreatopathy
D. Endocrinopathies
Acromegaly
Cushing's syndrome
Glucagonoma
Pheochromocytoma
Hyperthyroidism
Somatostatinoma
Aldosteronoma
E. Drug or chemical induced
Glucocorticoids
Thiazides
Statins
Antipsychotic medication
Antiretroviral therapy
Phenytoin
Thyroid hormone
F. Infections
Congenital rubella
Cytomegalovirus
G. Other genetic syndromes
Down syndrome
Klinefelter syndrome
Turner syndrome
Wolfram syndrome
Friedreich ataxia
Huntington chorea

Type 1 Diabetes Mellitus

Type 1 DM is characterized by complete cellular-mediated destruction of the β-cells, resulting in insulinopenia and insulin replacement therapy for survival. Majority of patients present with the constitutional symptoms of DM, namely, polyuria, polydipsia, and polyphagia. One-third of the patients can present with diabetic ketoacidosis as the first manifestation [31]. The disease is believed to be precipitated by an environmental insult in a genetically predisposed individual. Type 1 DM, including latent autoimmune diabetes in adults (LADA), is known to be strongly associated with human leukocyte antigen (HLA)-DR3-DQ2 and HLA-DR4-DQ8 haplotypes, alone or in combination [32, 33]. Some HLA haplotypes can offer protection from type 1 DM [34]. In addition, several other putative genes like cytotoxic T-lymphocyte-associated antigen 4, protein tyrosine phosphatase, non-receptor type 22, and insulin variable number tandem repeat affecting disease susceptibility have been identified [35]. Autoantibodies against islet antigens like glutamic acid decarboxylase 65, insulin, insulinoma-associated antigen 2 and 2β, and zinc transporter 8 are seen in the majority of patients [36, 37]. The number of antibody positivity correlates with the rate of progression of β-cell failure with 70% of children with two or more antibodies progressing to develop DM [38]. Three distinct stages of type 1 diabetes can be identified: presymptomatic with normoglycemia, presymptomatic with dysglycemia, and symptomatic with hyperglycemia [5]. In addition to islet cell autoimmunity, these patients are also predisposed to the development of other autoimmune disorders like Hashimoto's thyroiditis, Graves' disease, Addison's disease, celiac disease, vitiligo, autoimmune hepatitis, myasthenia gravis, and pernicious anemia [5].

A number of environmental triggers have been studied, including cow's milk, certain viruses, and gut microbiota, although none have been conclusively identified to influence the pathogenesis of type 1 diabetes mellitus [39–43]. A minority of patients with a clinical picture consistent with type 1 DM do not have evidence of autoimmunity. This is particularly common in patients of Asian and African ancestry and is not HLA-associated [44]. Ketosis-prone diabetes is an example of such a type of diabetes. There is currently a lack of accepted and clinically validated screening programs for type 1 DM outside of the research setting.

Type 2 Diabetes Mellitus

In contrast to type 1 diabetes, type 2 DM is characterized by relative insulin deficiency due to β-cell dysfunction and resistance to the action of insulin in target tissues. Unlike patients with type 1 DM, patients with type 2 DM, at least initially, are amenable to oral hypoglycemic agents. Beta-cell loss occurs progressively and can result in treatment failure with oral hypoglycemic agents and the requirement of insulin for the control of hyperglycemia, especially in younger individuals [45]. The global epidemic of type 2 diabetes mellitus parallels that of its prime risk factors—obesity, physical inactivity, and lifestyle modifications. Excessive abdominal adiposity, prior history of GDM, and certain ethnicities (like Asian, African American, Hispanic) are other strong risk factors for developing type 2 DM [5]. The ADA diabetes risk test (score ≥5) is an additional option for assessment to determine the appropriateness of testing for diabetes or prediabetes in asymptomatic adults (available on diabetes.org/socrisktest) based on age, gender, family history of diabetes, hypertension, GDM, physical inactivity, and obesity [5].

Gestational Diabetes Mellitus

GDM has traditionally been defined as any degree of glucose intolerance that is first detected during pregnancy, regardless of whether the condition may have predated the pregnancy or persisted after the pregnancy [46]. This definition of GDM, which is based on the PG level alone, does not distinguish the underlying pathological process. Hence, this heterogeneous group comprises women with preexisting insulin resistance and insulin deficiency worsened by deteriorating glucose homeostasis in pregnancy and women with short-term alterations in glucose homeostasis resulting from pregnancy-related physiological changes. Irrespective of the etiology, the management of these patients remains more or less the same, though women with pregestational diabetes need screening for long-term complications of dysglycemia, which can worsen further as pregnancy progresses [47].

The very first diagnostic criterion for GDM was proposed by O'Sullivan and Mahan in 1964. The authors had suggested a 50 g, 1-h glucose challenge test (GCT) for screening and follow-up of women with a 1-h post glucose load exceeding 140 mg/dL with a confirmatory test. A 100 g, 3-h OGTT was suggested to confirm the diagnosis. The cutoff levels were validated for the risk of the mother developing diabetes in the future and not for pregnancy outcomes [48].

This criterion was subsequently modified by the NDDG in the United States and later by Carpenter and Coustan to account for the changes in the methodology of glucose estimation and for using plasma samples instead of whole blood [3]. This modified criterion was widely accepted and endorsed by professional bodies like the ADA and WHO, until the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criterion was proposed, following the results of the path-breaking hyperglycemia and pregnancy outcomes (HAPO) study. The American College of

Obstetricians and Gynecologists (ACOG) still recommends the Carpenter and Coustan criterion [49].

HAPO was a large multinational, multicenter study which included over 23,000 pregnant women of diverse ethnicities. The OGTT was administered between 24 and 32 weeks of gestation using 75 g of glucose. A linear relationship was noted between PG levels following OGTT and several primary (umbilical cord-blood C peptide level, birth weight, neonatal hypoglycemia, and rate of cesarean delivery) and secondary outcomes (delivery before 37 weeks of gestation, shoulder dystocia or birth injury, need for intensive neonatal care, hyperbilirubinemia, and preeclampsia). The outcomes were directly related to FPG level and independently to 1-h and 2-h PG values [50].

Based on the results of the HAPO trial, IADPSG suggested a single-step, 75 g OGTT be performed in all pregnant women at 24–28 weeks of gestation. The defined diagnostic cut points for diagnosing GDM were those levels at which odds for adverse outcomes reached 1.75 times the estimated odds of these outcomes at the mean fasting, 1-h, and 2-h PG levels of the study population. A single value above the suggested cutoff was enough to make a diagnosis of GDM, unlike the two-abnormality criteria earlier followed [51].

Universal implementation of the stringent IADPSG criteria is likely to increase the prevalence of GDM as many women with mild GDM are likely to be included. The cost-effectiveness of this approach and its impact on improving maternal and fetal outcomes have been questioned. A few studies have however shown that the additional patients diagnosed using the IADPSG criterion when compared to other criteria are at risk for GDM-related complications [52–54]. The IADPSG also recommends diagnostic cutoff values to diagnose GDM in the first trimester. This recommendation was not based on any hard data and was an extrapolation of the results of the HAPO study. In 2011, the ADA also adopted the IADPSG criteria.

The NICE in 2015 published its guidelines for diagnosing GDM and suggested higher FPG cutoff values when compared to those of the IADPSG. The prime reason quoted for choosing higher FPG levels was to reduce the economic burden imposed by the application of a lower FPG cutoff on the health-care system. Though this criterion strives to strike a middle ground, it has not been tested clinically, and its impact on maternal and fetal health will be seen in the coming years [55]. The cutoff values for diagnosing GDM using the one-step and two-step strategies according to the ADA are given below [5].

One-Step Strategy

75-g OGTT is recommended with PG measurement when the patient is fasting and, at 1 h and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes. The OGTT should be performed in the morning after an overnight fast of at least 8 h. The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- FPG: 92 mg/dL (5.1 mmol/L)
- 1-h PG: 180 mg/dL (10.0 mmol/L)
- 2-h PG: 153 mg/dL (8.5 mmol/L)

Two-Step Strategy

Step 1

Perform a 50-g GCT (non-fasting), with PG measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes. If the PG level measured 1 h after the load is ≥130, ≥135, or ≥140 mg/dL (7.2, 7.5, or 7.8 mmol/L), proceed to a 100-g OGTT. The ACOG recommends either of the commonly used thresholds of 130, 135, or 140 mg/dL for the 1-h 50-g GCT.

Step 2

The 100-g OGTT should be performed when the patient is fasting. The diagnosis of GDM is made if at least two of the following four plasma glucose levels (measured at fasting and 1, 2, 3 h after the OGTT) are met or exceeded. However, the ACOG notes that one elevated value can be used for diagnosis:

- FPG: 95 mg/dL (5.3 mmol/L)
- 1-h PG: 180 mg/dL (10.0 mmol/L)
- 2-h PG: 155 mg/dL (8.6 mmol/L)
- 3-h PG: 140 mg/dL (7.8 mmol/L)

Screening for GDM

Recommendations for choosing the target population for GDM screening are shrouded by controversies and a lack of uniformity among the existing guidelines. The WHO and ADA recommend universal screening of all pregnant women, while the NICE guidelines recommend a selective screening strategy [55, 56]. The selective screening approach is likely to miss a significant proportion of women who develop GDM in the absence of traditional risk factors [57, 58]. The ADA recommends screening for diabetes in women with risk factors for diabetes at the first prenatal visit using its standard diagnostic criteria. Those who are not known to have diabetes are to be screened at 24–28 weeks of gestation using a one-step or a two-step approach [5].

Screening for Persistent Diabetes After Pregnancy

The majority of women diagnosed with GDM will revert to normalcy in the immediate postpartum period, leaving a small proportion with continuing hyperglycemia. The lifetime risk

of developing type 2 DM is as high as 50–70% [59]. The immediate postnatal period provides a window of opportunity to identify this precarious cohort of at-risk women. The ADA recommends screening at 4–12 weeks postpartum using the OGTT and advises lifelong follow-up and screening at least every 3 years [5]. The NICE guidelines recommend using FPG or HBA1c after 13 weeks, and annual testing with HbA1c is recommended if the first test is normal [55].

Specific Types of Diabetes Due to Other Causes

This heterogeneous group includes monogenic forms of diabetes and others with an underlying genetic defect affecting insulin secretion and action, diseases affecting the pancreas, diabetes associated with endocrine disorders, drug-induced diabetes, and posttransplantation diabetes.

Monogenic Diabetes Syndromes

Single gene defects causing β-cell dysfunction constitute around 1–2% of all cases of DM [60]. MODY is characterized by defective insulin secretion with intact insulin action. Thirteen different genetic loci have been identified so far and are inherited in an autosomal dominant fashion [5]. The most commonly reported types include MODY 2, MODY 3, and MODY 1. There is wide variation in the severity and clinical course of the disease among the various types. Some forms show excellent response to sulfonylurea, and certain subtypes require insulin therapy for management. Identification of additional malformations or multisystem involvement helps in arriving at a diagnosis and also necessitates a multipronged approach to the management of these patients.

Neonatal Diabetes

Infants developing DM within the first 6 months of life should undergo genetic testing to identify potential genetic defects. Neonatal diabetes can be transient or permanent, and patients who have an initial transient presentation can develop DM later in life. Making the correct diagnosis in these patients cannot be overemphasized, as switching to oral hypoglycemic agents is possible in a subset of them with potassium inwardly rectifying channel, subfamily J, member 11 (KCNJ11), and ATP-binding cassette, subfamily C, member 8 (ABCC8) mutations, thus greatly reducing the burden of management on the afflicted family [61, 62].

Diabetes Mellitus Secondary to Pancreatic Disorders

Acute and Chronic Pancreatitis

Acute pancreatitis often results in defective glucose metabolism at presentation. In many patients, this defect is transient. However, the risk of developing DM is increased during the follow-up of these patients. Chronic inflammation and destruction of pancreatic tissue can occur due to several etiologies, including cystic fibrosis-related diabetes. Although the islets are more resistant to the destructive process in the earlier stages, significant β-cell loss eventually ensues, resulting in varying degrees of dysglycemia.

Fibrocalculous Pancreatitis

Tropical chronic pancreatitis, or fibrocalculous pancreatic diabetes (FCPD), is a specific form of chronic pancreatitis which is encountered in several tropical countries, as the name suggests. The etiology of this condition is elusive, and a number of hypotheses exist to explain its occurrence. The earlier popular theories linking the consumption of cassava with FCPD have been challenged [63]. Familial clustering of cases makes genetic predisposition a plausible risk factor. Several candidate genes have been explored in this context, with the most prominent ones being serum protease inhibitor Kazal type 1 (SPINK1), cationic trypsinogen (PRSS1), anionic trypsinogen (PRSS2), and chymotrypsinogen C [64, 65]. Increased oxidative stress has also been reported in patients with FCPD [66].

Almost 90% of patients develop diabetes eventually due to β-cell destruction [67]. Although defective insulin secretion is a cardinal defect, the development of insulin resistance is also known [68]. Defects in the shifting of glucose transporter 2 (GLUT2) into the hepatocyte membranes during the postabsorptive phase have been shown in animal models of chronic pancreatitis. This can result in postprandial glucose excursions [69]. Also, pancreatic polypeptide secreted by the islet cells plays a role in the expression of the insulin receptor gene in the liver. Deficiency of pancreatic polypeptide, along with insulin deficiency, could contribute to the development of diabetes [70]. Glucagon levels, on the other hand, have been postulated to be relatively unaffected or even elevated in a few studies, indicating selective destruction of the islet cells [71, 72]. However, not all studies corroborate this theory, and it needs further analysis.

In patients presenting with symptoms of chronic pancreatitis, typical large ductal calcifications and dilatation of the pancreatic ducts visualized on imaging point to a diagnosis of FCPD. Diabetes in this scenario is generally ketosis-resistant with most patients requiring insulin therapy [68, 72]. Most patients also have evidence of exocrine pancreatic insufficiency at the time of diagnosis, and enzyme replacement therapy can worsen glycemic control by improving malabsorption.

Pancreatic Ductal Adenocarcinoma

The relationship between pancreatic ductal adenocarcinoma (PDAC) and DM is complex. DM is believed to be a risk factor for developing PDAC, while the malignancy per se

has been postulated to affect glucose homeostasis. Around 85% of patients with PDAC have IGT or DM [73]. A meta-analysis of 36 studies indicated that the risk of developing PDAC is twofold higher in patients with DM [74]. Also, studies show that 25–50% of patients with PDAC develop diabetes in the preceding 1–3 years of their diagnosis [75]. Pancreatitis related to the tumor, destruction of islets, and the development of insulin resistance are the postulated mechanisms to explain the development of diabetes. Animal studies suggest that the secretory products of tumor cells can impair glucose metabolism [76]. New-onset DM in these patients is known to improve with resection of the tumor, further strengthening the link between the two [73].

Endocrinopathies

Acromegaly

Majority of patients with acromegaly are diagnosed with either prediabetes or diabetes at presentation. The reported prevalence of prediabetes varies between 16% and 46% [77–79], and that of DM is between 15% and 38% [80]. The risk of developing diabetes is strongly associated with higher growth hormone (GH) levels, family history of diabetes, hypertension, increasing age, and disease duration [79, 80]. Identification and appropriate management of diabetes are essential to preventing the increased cardiovascular morbidity and mortality associated with it.

GH plays an important role in regulating intermediary metabolism. It stimulates lipolysis, suppresses lipogenesis, and also antagonizes the insulin-induced suppression of gluconeogenesis, resulting in increased hepatic glucose output [81, 82]. Increased levels of free fatty acids induce a state of insulin resistance in the liver and peripheral tissues [83]. The inability of the β-cells to compensate for this state of insulin resistance results in the development of diabetes. Direct inhibition of insulin signaling by interfering with downstream signaling molecules like insulin receptor substrate-1 (IRS-1) and phosphatidylinositol 3 (Pi-3) kinase also contributes to the development of diabetes [84]. Most patients with acromegaly undergo surgical resection and radiotherapy. Some, in addition, require medical management for ameliorating disease activity. The treatment modality chosen can also influence the glycemic status. Surgical removal of the tumor and subsequent reduction of GH and insulin-like growth factor-1 levels are associated with improvement of glycemic status [85, 86]. Dopamine agonists have a modest effect on reducing PG levels, and the effect of somatostatin agonists (SSA) on glucose metabolism is conflicting [87]. SSA can inhibit insulin and incretin secretion and worsen glucose levels, especially in those with an underlying insulin secretion defect, though this is often offset by the reduction in GH level and improvement of disease status [87]. Among the SSA, pasireotide seems to have a greater propensity to alter glycemic control, and its effect is dose-dependent. This tendency can be explained by its greater affinity for somatostatin receptor subtype 5 expressed in the islet cells when compared to other SSA [88]. Pegvisomant is another agent which can improve glycemic control by containing disease activity. There is a reduction in FPG levels, and improved insulin sensitivity has been noted in most studies [87].

Cushing's Syndrome

Glucocorticoids exert a multitude of effects on the various organs involved in carbohydrate metabolism. It stimulates lipoprotein lipase activity and lipolysis [89]. At the liver, increased glucose output results from an increased rate of gluconeogenesis. These actions, in addition to reduced glucose uptake by muscles and increased proteolysis, result in a state of insulin resistance [90, 91]. Reduced expression of glucokinase and GLUT2 in the pancreatic β-cells results in reduced insulin secretion, which compounds the diabetogenic action of glucocorticoids [92]. Glucocorticoids can interfere with the action of insulin directly by inhibiting downstream signaling molecules like IRS-1 and Pi-3 kinase [93, 94]. Disordered glucose metabolism is seen in 50% of patients with endogenous Cushing's syndrome, with two-thirds of them developing diabetes [95, 96]. Increased prevalence of diabetes and prediabetes is also observed in cases of adrenal incidentaloma associated with subclinical Cushing's syndrome [97]. Glucose metabolism generally improves with cure, though these patients seem to have a continuing greater risk of cardiovascular morbidity. Most drugs used in the management of Cushing's syndrome, like ketoconazole, dopamine agonists, and metyrapone, have a favorable effect on glycemic control. Pasireotide, on the other hand, is known to worsen hyperglycemia [87]. The frequency of hyperglycemia-related adverse effects is lower in patients with acromegaly who are treated with pasireotide long-acting release (57.3–67%) than those with Cushing's syndrome who are treated with the subcutaneous formulation (68.4–73%) [98].

Treatment with metformin is recommended as first-line therapy for patients on pasireotide with persistent hyperglycemia. A dipeptidyl peptidase-4 inhibitor can be added on in patients failing monotherapy with metformin. A glucagon-like peptide-1 receptor agonist should be added in place of the dipeptidyl peptidase-4 inhibitor if HbA1C continues to remain above 7.0%. Insulin is started as a final resort if adequate glycemic control is not achieved with the above measures [98].

Other Endocrine Disorders

Glucagonoma

Islet cell tumors secreting glucagon are rare with a reported incidence of 0.04–0.12 per million per year [99]. They are

exclusively seen in the pancreas with the tail being the most common location [100]. In two-thirds of the cases, the tumor is malignant, and half of them have evidence of metastasis at the time of diagnosis [101]. DM is known to occur in 40–95% of patients, along with other symptoms like weight loss, gastrointestinal manifestations, and neurological symptoms like ataxia, dementia, optic atrophy, and proximal muscle weakness [102, 103]. The characteristic dermatological lesion called necrolytic migratory erythema is seen in 90% of patients. Glucagon increases hepatic gluconeogenesis and also increases lipolysis and fatty acid oxidation [104]. Diabetes mellitus is generally mild and nonketotic.

Somatostatinoma

Somatostatinomas are rarer than glucagonomas and occur in less than 1 in 40 million people [105]. They produce excess somatostatin, which directly suppresses insulin and glucagon secretion, causing diabetes. The most common clinical manifestation is related to mass effects, and metabolic manifestations occur in a minority [103, 106].

Drug-Induced Diabetes Mellitus

Thiazide Diuretics

Studies reporting the incidence of diabetes with thiazide diuretics have been conflicting. A recent meta-analysis of 22 studies showed an increased risk of diabetes with thiazides and beta-blockers when compared to other antihypertensive agents like angiotensin-converting enzyme inhibitors and angiotensin receptor blockers [107]. Hypokalemia caused by thiazides has been linked to impaired insulin secretion in addition to other mechanisms like decreased insulin sensitivity, increased hepatic glucose production, alteration in body fat composition, and stimulation of glucagon [108, 109].

Statins

Statins are widely used as the first choice for their potent low-density lipoprotein-lowering effect. Evidence for their diabetogenic potential was first demonstrated in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial in which a 32% increased risk of new-onset diabetes was noted in the statin arm [110]. Subsequently, similar risks for diabetes have been reported for other statins, prompting the Food and Drug Administration (FDA) in 2012 to add a warning of the increased risk of diabetes with statin use. A meta-analysis of 113,394 subjects showed a 15% added risk of new-onset diabetes with 80 mg of atorvastatin and 25% with rosuvastatin at a dose of 20 mg [111]. Statins are also known to worsen glycemic control in patients with DM. The risk for DM with statins is more pronounced in those who already have the traditional risk factors. Mechanisms by which statins induce and aggravate diabetes include impaired pancreatic secretion of insulin (by blocking calcium channels), reduced expression of GLUT4 interfering with glucose uptake and disposal by skeletal muscle, and exacerbation of insulin resistance in liver and peripheral tissues [112]. Lipophilic statins like simvastatin and atorvastatin are transported across cellular membranes with ease, explaining their greater propensity to cause diabetes [113].

Beta-Blockers

β-Blockers impair insulin secretion, increase hepatic glucose production, and impair lipoprotein clearance. The risk of diabetes is higher with nonselective beta-blockers [108, 114].

Antipsychotic Medications

Weight gain is a common adverse effect of almost all antipsychotic medications. The magnitude of weight gain varies with the different drugs, and the greatest risk is associated with clozapine and olanzapine [115]. Aripiprazole has a minimal effect on weight gain [116]. Maximum weight gain occurs in the first year of therapy and is related to the duration of exposure. Increased appetite and consequent food intake, reduced satiety, and effects on adipose tissue like increased lipogenesis contribute to weight gain [117, 118].

The risk for diabetes is also greater, especially with second-generation antipsychotics. It is estimated to be 32% higher in this group. Drugs causing increased weight gain are associated with a greater risk for diabetes. In some patients, this effect seems to be independent of the change in body weight. Blockage of muscarinic receptor 3 by antipsychotic medication is known, and this can hamper insulin secretion [119]. Impaired insulin sensitivity in peripheral tissues is also known to occur, possibly by interfering with the functioning of glucose transporters [118].

Antiretroviral Therapy

Risk of new-onset diabetes is a well-known complication of antiretroviral therapy, particularly with stavudine, indinavir, and didanosine. The drugs per se and the lipodystrophy associated with their use contribute to metabolic derangements. PG abnormalities are seen in 25% of patients following the initiation of protease inhibitors. Redistribution of adipose tissue is the key factor contributing to increased insulin resistance. Age, BMI, and waist circumference are additional risk factors [120–122].

Posttransplantation Diabetes Mellitus

Posttransplantation diabetes mellitus describes the presence of diabetes in the posttransplant setting, irrespective of the timing of diabetes onset. New-onset diabetes after transplantation (NODAT) refers to the occurrence of diabetes in previously nondiabetic persons after organ transplantation. NODAT excludes patients with pretransplant diabetes that was undiagnosed as well as posttransplant hyperglycemia that resolves by the time of discharge. Twenty percent to 50% of patients following kidney transplants, 9–21% after

liver transplants, and approximately 20% after lung transplants are diagnosed to have NODAT at 12 months post-transplant [123]. NODAT increases the risk of allograft loss, infections, and mortality in post-renal transplant recipients [124–127]. Patients with NODAT also develop microvascular complications associated with diabetes at an accelerated rate and are at an increased risk for cardiovascular morbidity and mortality [128]. In addition to the traditional risk factors for DM, exposure to immunosuppressive agents, CMV and hepatitis C infection, and acute rejection posttransplantation augment the risk of developing NODAT [129–132].

The ADA recommends screening for hyperglycemia in all patients posttransplantation using OGTT. A diagnosis of NODAT can be made using the standard criteria if the patient is on a stable immunosuppressive regimen and is free from infections [5].

Concluding Remarks

- Diabetes mellitus is a global epidemic and is associated with multiple morbidities and mortality. The importance of adequate glycemic control in order to circumvent these complications has been proven beyond doubt. However, there still exists a controversy over the appropriate diagnostic criteria for diabetes mellitus and prediabetes, which is constantly evolving.
- Diabetes mellitus is the final common outcome of disrupted insulin secretion and/or action. An array of etiologies is known to cause this disruption, ranging from monogenic and polygenic predispositions to endocrinopathies and drug therapy.
- Prediabetes is an intermediate state of hyperglycemia and includes the states of impaired fasting glucose and impaired glucose tolerance. The rise in the incidence of prediabetes globally mirrors that of diabetes mellitus. Screening for and detection of prediabetes is an opportunity to intervene and prevent the progression of diabetes mellitus and its complications.
- Gestational diabetes mellitus is defined as any degree of hyperglycemia that is first detected during pregnancy and encompasses true gestational diabetes mellitus and preexisting diabetes mellitus. There is no universal criteria for diagnosing GDM. Several countries have adopted differing criteria that best meet the needs of their populations.

Multiple-Choice Questions

1. Falsely low HBA1c levels can be seen in all of the following conditions except:
   (a) Hemolytic anemia
   (b) Hypertriglyceridemia
   (c) **Postsplenectomy**
   (d) Renal failure
   (e) Malaria
2. Maturity-onset diabetes in the young is inherited in _____ fashion.
   (a) Autosomal recessive
   (b) **Autosomal dominant**
   (c) X-linked dominant
   (d) X-linked recessive
   (e) Mitochondrial
3. Which of the following treatment modalities for acromegaly can worsen glycemic control?
   (a) Surgery
   (b) Radiotherapy
   (c) Dopamine agonists
   (d) **Pasireotide**
   (e) Pegvisomant
4. Glucocorticoid excess results in diabetes mellitus through which of the following mechanisms?
   (a) Stimulating lipolysis
   (b) Increasing rate of gluconeogenesis
   (c) Inducing a state of insulin resistance
   (d) Interfering with the action of insulin by affecting down-stream signaling molecules
   (e) **All of the above**
5. Which of the following drugs are known to cause or worsen diabetes mellitus?
   (a) Dopamine agonists
   (b) **Thiazides**
   (c) Loop diuretics
   (d) Alpha-adrenergic blockers
   (e) All of the above
6. Genetic syndrome associated with diabetes mellitus is
   (a) **Turner syndrome**
   (b) Edward syndrome
   (c) Patau syndrome
   (d) Cri du chat syndrome
   (e) **Down syndrome**
7. Endocrinopathy associated with secondary diabetes is
   (a) Adrenal insufficiency
   (b) **Somatostatinoma**
   (c) **Hyperthyroidism**
   (d) Hypoparathyroidism
   (e) Insulinoma

8. ADA recommendations to begin screening for diabetes mellitus for all patients at age.
   (a) 40 years
   (b) **45 years**
   (c) 50 years
   (d) 35 years
   (e) 55 years
9. The rate of progression of prediabetes to diabetes mellitus in the absence of intervention is
   (a) 1–2% per year
   (b) **5–10% per year**
   (c) 20% per year
   (d) 40% per year
   (e) 60% per year
10. The HbA1c cutoff recommended by the ADA for diagnosing diabetes mellitus is
   (a) ≥5.7%
   (b) ≥6.7%
   (c) ≥7%
   (d) ≥7.5%
   (e) **≥6.5%**

Glossary

Diabetes mellitus Diabetes is derived from its Greek root, which means "to pass through," and the word mellitus means "from honey." Diabetes mellitus is defined by the World Health Organization as a metabolic syndrome characterized by chronic hyperglycemia resulting from any of the several conditions that cause defective insulin secretion and/or action.

Gestational diabetes mellitus Defined as any degree of glucose intolerance that was first detected during pregnancy, regardless of whether the condition may have predated the pregnancy or persisted after the pregnancy.

Impaired glucose tolerance Defined as an intermediate state where blood glucose levels are above normal but do not satisfy the criteria for diagnosing diabetes mellitus.

Neonatal diabetes Development of diabetes in the first 6 months of life.

NODAT (new-onset diabetes after transplantation) Defined as the occurrence of diabetes in previously nondiabetic persons after organ transplantation.

Prediabetes It is a state characterized by metabolic abnormalities that increase the risk of developing diabetes mellitus and its complications.

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7 Homeostasis of Glucose and Intermediate Metabolism: From the Lens of a Clinician

Nitin Kapoor and Madhukar Mittal

Introduction

The key substrate for energy production is blood glucose during all the phases of life. Fasting blood glucose levels remain within a narrow physiological range of 70-100 mg/dL except in the first few days of life and during pregnancy [1]. There are variations in blood glucose levels beyond this range as revealed by continuous glucose monitoring systems, which show levels both high and low (especially post meal excursions being greater), but this change spontaneously reverts to within the normal range rapidly. Both fasting and postprandial blood glucose levels are kept within a tightly controlled range. This glucose homeostasis is the result of a complex interplay of hormones controlling glucose production and glucose utilisation, which include insulin, glucagon, epinephrine, norepinephrine, cortisol and human growth hormone (HGH) [2]. Most of these hormones help maintain blood glucose levels in the fasting state while it is mainly the insulin and the incretin hormones that help regulate levels in the postprandial state. The early line of defence against hypoglycaemia includes glucagon and epinephrine, while cortisol and HGH rise in a more gradual way.

Although Claude Bernard introduced the concept of homeostasis, it was Walter Canon who introduced the term "homeostasis," defining it as "the various physiologic arrangements that serve to restore the normal state, once it has been disturbed" and expanded on the foundations laid by Bernard [3]. Glucose homeostasis, as the name suggests, is the process of maintaining blood glucose levels at a steady-state. After a meal, this is accomplished by an intricately driven and balanced hormonal regulation of glucose absorption, peripheral glucose uptake and hepatic glucose production.

The liver produces glucose through glycogenolysis (breakdown of stored glycogen) and gluconeogenesis (formation of glucose from non-carbohydrate sources such as lactate, alanine and glycerol). Apart from the liver, the kidney also plays an important role as a gluconeogenic organ. This chapter discusses the phases of glucose homeostasis, the various metabolic pathways, glucose transporters, the various organ systems and glucose homeostasis in hypoglycaemic disorders.

In healthy individuals after a meal, the liver is a major site of glucose utilisation (30-60% of the ingested glucose). Glucose uptake in skeletal muscle and in non-insulin-sensitive tissues like the brain, accounts for the rest of the total glucose disposal in the postprandial state. Glucose provides reducing equivalents for fatty acid synthesis, ribose 5-phosphate for nucleotide synthesis and precursors for glycosylation reactions. Glucose enters the liver cells and is phosphorylated to glucose 6-phosphate. Glucose 6-phosphate is like a central hub for carbohydrate metabolism and may follow a number of metabolic pathways, including glycolysis, glycogen synthesis, the hexosamine pathway, the pentose phosphate pathway and oxidative routes based on the nutritional or hormonal status of an individual.

Phases of Glucose Homeostasis

Normal glucose homeostasis after food intake requires the maintenance of the closely coordinated effects of insulin in conjunction with other hormones to stimulate glucose uptake by peripheral tissues, stimulate glucose uptake by the liver, suppress hepatic glucose production, inhibit lipolysis and reduce FFA concentration. The five phases of glucose homeostasis are described below and summarised in Table 7.1 [4].

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Table 7.1 Phases of glucose homeostasis

	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
Origin of blood glucose	Exogenous	Glycogen predominantly	Gluconeogenesis (hepatic) glycogen	Gluconeogenesis (hepatic and renal)	Gluconeogenesis (hepatic and renal)
Time interval	2-4 h	4-16 h	16-48 h	2-5 Days	>5 days
Tissues utilising	All	All except liver	All except liver	Brain, RBCs, renal medulla	Brain at diminished rates
Glucose		Muscle and adipose tissue at reduced rates	Muscle and adipose tissue at reduced rates		
Major fuel for brain	Glucose	Glucose	Glucose	Glucose + ketone bodies	Glucose + ketone bodies

1. Absorptive (Well-fed State)
   (a) Occurs within 2-4 hours of food intake
   (b) Maintenance of euglycemia is dependent on five processes that occur in a simultaneous and coordinated fashion:
   (c) Plasma levels of glucose, amino acids and triacylglycerols increase
   (d) Insulin secretion is stimulated in response to hyperglycaemia
   (e) Hyperinsulinemia along with hyperglycaemia augments glucose uptake by splanchnic (liver and gut) and peripheral tissues (primarily muscle and adipose tissues)
   (f) Hepatic glucose production is further suppressed by insulin and hyperglycemia
   (g) Lipolysis in adipocytes is inhibited by insulin, and the subsequent reduction in FFA further augments muscle glucose uptake and facilitates the suppression of glucose production
2. Early Fasting
   (a) Occurs 4-16 hours after food intake
   (b) Glucose homeostasis shifts from energy storage to production with an accompanying decrease in insulin levels and a rise in glucagon levels that typically occur after an overnight fast.
   (c) This phase predominantly involves glycogenolysis
   (d) Maintains blood glucose levels for 16-18 hours
3. Fasting (Gluconeogenic)
   (a) Occurs 16-48 hours after food intake
   (b) Gluconeogenesis is the predominant pathway to occur in this phase
   (c) The required ATP for gluconeogenesis is provided by fatty acid oxidation of triacylglycerol in this phase
4. Prolonged Fasting or Starvation
   (a) Occurs 2-5 days after food intake
   (b) Decreased gluconeogenesis
   (c) There is splitting of triacylglycerol into fatty acids, which undergo beta oxidation to produce acetylcoA, which subsequently forms ketone bodies
   (d) The presence of ketone bodies prevents muscle proteolysis
5. Prolonged Starvation
   (a) Occurs after more than 5 days of fasting
   (b) Decreased fatty acid oxidation along with decreased ketone body synthesis
   (c) Lysis of muscle proteins: cachexia

From an evolutionary perspective, there has been an adaptation of the physiological processes in humans for survival, even in prolonged periods of fasting. With progressive fasting, there occurs a switch of major fuel for the body's utilisation from glucose, derived from glycogenolysis and gluconeogenesis, to fatty acids and ketone bodies termed the "flipping of the metabolic switch". The hormonal changes mediating these changes include suppression of insulin along with raised concentrations of counterregulatory hormones involving glucagon, cortisol, growth hormone and cortisol.

Depending on the individual's energy expenditure/exercise during the fast, liver glycogen content, the metabolic switch typically occurs in the third phase of fasting, between 12 and 36 hours after cessation of food consumption, and is characterised by the depletion of glycogen stores and accelerated lipolysis, which produces increased fatty acids and glycerol. Free fatty acids are then transported into hepatocytes and metabolised by β-oxidation to produce ketones, namely, beta-hydroxy butyrate, acetone and acetoacetate. These are transported into cells with high metabolic activity and metabolised to acetyl CoA, which then enters the TCA cycle to generate ATP. Hence they function as energy generating fuels, especially in the brain, during periods of prolonged fasting when there is limited glucose availability.

Fasting, initially a survival trait, has since been used as a religious and medical practise with improved nutrient availability for thousands of years. This cuts across geographical landscapes, religions and cultures, with a multitude of durations and formats. The potential benefits of fasting described in literature involve an improvement in insulin sensitivity, a decrease in inflammatory cytokines, an improvement in lipid profiles, weight loss, and a wide variety of other benefits. Case reports have been described utilising fasting for the management of both type 1 and type 2 diabetes. It becomes important, however, to balance out these potential benefits against the downside of extreme fasting and starvation, like nausea, vomiting, alopecia, motor neuropathy, hyperuricemia and urate nephropathy, deranged liver functions, metabolic acidosis and Wernicke encephalopathy.

Glucose Pathways in Health and Disease (Figs. 7.1 and 7.2)

Broadly, the various metabolic pathways can be grouped into four categories as follows [5]:

1. Glycolysis, fructose/galactose metabolism, the tricarboxylic acid (TCA) cycle and oxidative phosphorylation are pathways that release energy
2. Glycogenesis and lipid synthesis are pathways of energy storage
3. Gluconeogenesis, lipolysis, glycogenolysis and protein catabolism occur in states of starvation
4. Pentose phosphate pathway (HMP shunt), urea cycle and cholesterol synthesis are the other pathways

Metabolic pathways maintaining glucose homeostasis (Table 7.2) can be generally categorised as "fed-state" or "fasting-state" based on whether they build energy reserves or release energy for later use.

Glycolysis (Embden-Meyerhof-Parnas Pathway)

Being one of the major metabolic pathways for glucose metabolism, it operates in all the cells of the body. Glycolysis, is unique in that it functions both aerobically and anaerobically. As the name suggests, in glycolysis, there is lysis of the 6-carbon glucose into two 3-carbon compounds: dihydoxyacetone phosphate and glyceraldehyde-3-phosphate. This glyceraldehyde-3-phosphate is then further catalyzed or converted via a series of steps to pyruvate. The fate of pyruvate further depends on the body's needs: In presence of oxygen, pyruvate is metabolised to acetyl CoA and further enters the Krebs cycle and the electron transport chain. In the absence of oxygen, however, it is converted to lactate via lactate

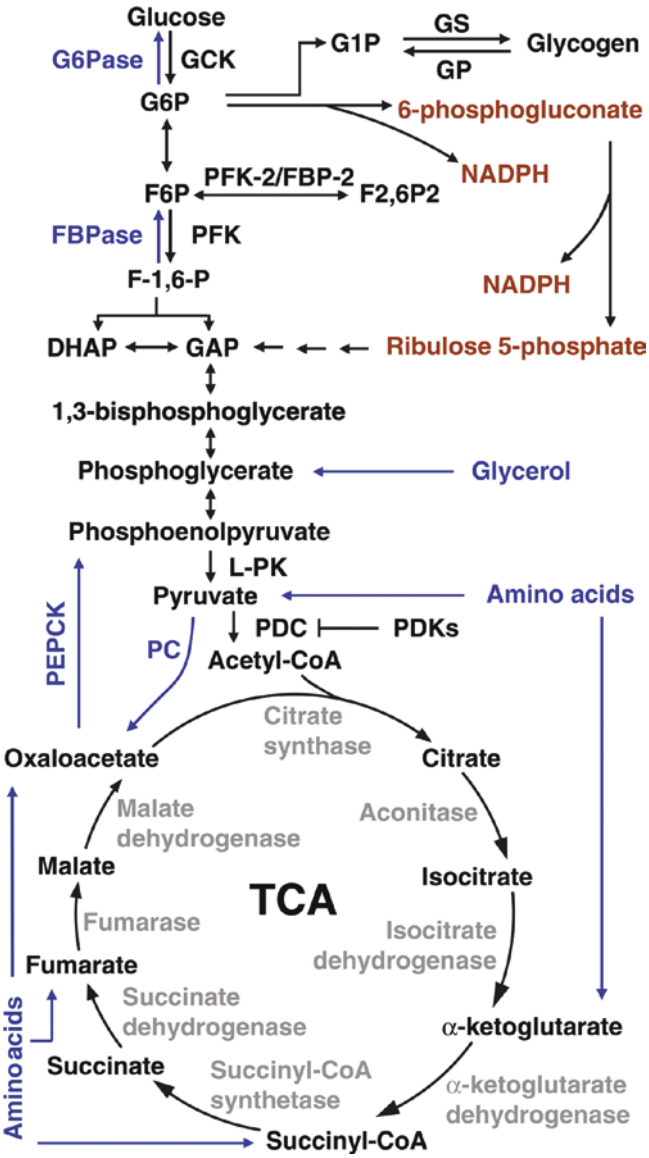

Fig. 7.2 Glucose metabolic pathways

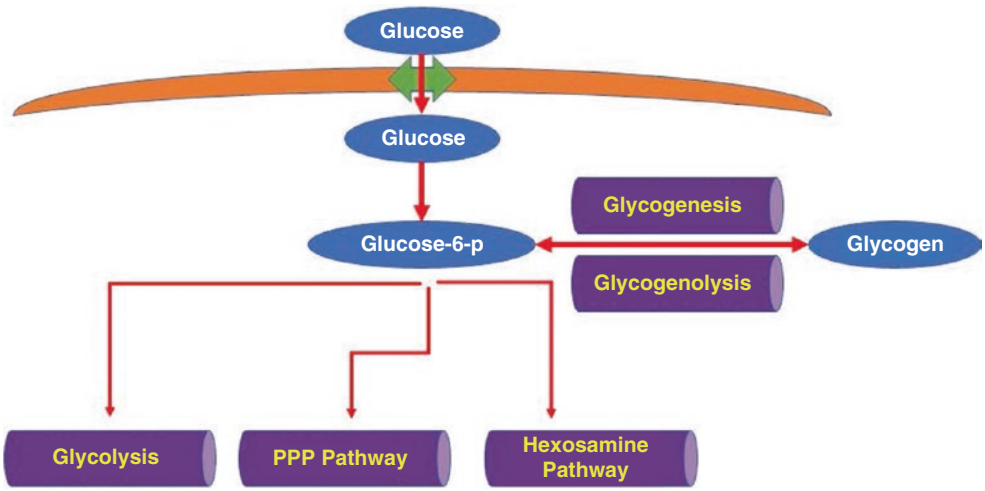

Fig. 7.1 Major Glucose metabolic pathways (⇔ glucose transporter)

Table 7.2 Metabolic processes in fasting and fed states

Fed state	Fasting state
Glycolysis	Glycogenolysis
Glycogenesis	Gluconeogenesis
Lipogenesis	Lipolysis
Fructose/galactose catabolism	Protein catabolism
	Ketone body metabolism

dehydrogenase. In terms of energetics, aerobic glycolysis leads to the generation of net 7 ATPs in comparison to anaerobic glycolysis which generates net 2 ATPs [6, 7].

Regulation of glycolysis: In the fed state, under the influence of insulin, glycolytic hormones are active due to the presence of insulin, while in the fasting state, enzymes are inactive due to the presence of glucagon.

Clinical Relevance

- In RBCs, due to the absence of mitochondria, anaerobic glycolysis occurs predominantly. Ten percent of glucose entering the RBCs is metabolised via the Rapaport Leubering cycle, where 1,3 BPG is converted to 2,3 BPG via bisphosphoglycerate mutase, which is then converted to 3 PG via phosphatase. No ATP is produced via this pathway, the significance of this pathway, however, lies in the fact that 2,3 BPG shifts the oxygen dissociation curve to the right and helps with oxygen unloading at the tissue level [6].

- In cancer cells, pyruvate kinase M2 (low catalytic activity) converts pyruvate to lactate, in contrast to pyruvate kinase M1, which functions in normal glycolysis. Hence, this consumption of oxygen by cancer cells leading to the generation of lactate is called aerobic glycolysis. This forms the basis of functional PET scanning, where cancer cells will take up all the glucose that is available. Warburg effect: Via Oto Warburg, in 1924, he stated that cancer cells use more glucose and convert it to lactate in the presence of oxygen. He, however, proposed that this was due to a defect in the mitochondrial respiratory chain, while it has now been seen that this effect is due to metabolic reprogramming.
- Inhibitors of glycolysis: arsenate inhibits glyceraldehyde 3 phosphate via decreased availability of inorganic phosphate. Fluoride inhibits the enzyme Enolase, the significance is that when blood is drawn for glucose estimation, the presence of fluoride inhibits glycolysis, preventing a fall in blood glucose levels post collection.

- Deficiency of enzymes of glycolysis leads to hemolysis, Pyruvate kinase deficiency is the second most common enzyme deficiency in humans and its absence leads to hemolysis. Similarly, aldolase An enzyme deficiency leads to hemolysis, while a muscle PFKI deficiency causes exercise intolerance.

Gluconeogenesis

The importance of gluconeogenesis lies during fasting. In the early stages of fasting, that is, from 4 to 16 hours, glycogenolysis predominates and maintains blood glucose levels for 16-18 hours. After 16-48 hours of fasting, gluconeogenesis predominates, which implies the synthesis of glucose from noncarbohydrate substrates. It occurs predominantly in the liver and kidney. The substrates for gluconeogenesis are predominantly alanine, lactate, glycerol and propionyl CoA [6].

- Lactate (Cori's cycle): In skeletal muscle, the glucose is converted to lactate, which in the liver is metabolised to glucose, and this glucose is then metabolised in the muscle.
- Alanine (Cahill cycle): The importance of this cycle occurs in starvation. Glucose in muscle is converted to pyruvate, which is transaminated to alanine, which then enters the liver; alanine is then converted to glucose.
- Glycerol: It is converted to glycerol-3-phosphate which is then converted to DHAP which is then metabolised to glucose.
- Propionyl CoA: It is converted to glucose via methymalonyl CoA and succinyl CoA, which act as intermediates.
- Regulation: In the well-fed state, glycolysis is active. In the fasting state, under the influence of glucagon, gluconeogenesis is switched on. Acetyl CoA is an allosteric activator of pyruvate carboxylase, one of the key enzymes of gluconeogenesis. Fructose- 2,6-bisphosphate is an allosteric inhibitor of fructose-1,6-bisphosphatase and an activator of PFK-1.

Glycogen Metabolism

Glycogen, the storage form of glucose in animals, is composed of glucose residues joined in straight chains by alpha 1,4 linkages and branched at intervals of 4-10 residues by alpha 1,6 linkages.

Glycogenesis

In a well-fed state, insulin stimulates glycogenesis. It occurs in the liver and muscles in the cytosol. The rate-limiting enzyme of glycogen synthesis is glycogen synthase. It occurs with the formation of UDG Glucose which functions as the active glucose donor. Glucose is converted to glucose-6-phosphate via hexokinase, a step common to both glycolysis

and glycogenesis. Glucose-6-phosphate is then converted to glucose-1-phosphate which donates the glucose to UTP, forming UDG Glucose. Glycogenin, a 37 kDa polypeptide with tyrosine residues, functions as the primer for glycogen synthesis. Glycogen synthase, via its alpha 1,4 action, helps to add glucose residues in a linear fashion. For the formation of branching points, alpha 1,4-alpha 1,6 glucan transferase is needed [6].

Glycogenolysis

In the early fasting stage, under the influence of glucagon, glycogenolysis occurs predominantly in the liver and the cytosol. The rate limiting enzyme here is glycogen phosphorylase, which releases glucose as glucose-1-phosphate. Following this, the debranching enzyme, which functions as alpha 1,4-1,4 glucan transferase and alpha 1,6 glucosidase, is produced. Glucose-1-phosphate is converted to glucose-6-phosphate, which is eventually converted to glucose in the liver [6].

Pentose Phosphate Pathway (PPP), Phosphogluconate Pathway or Hexose Monophosphate (HMP) Shunt

The pentose phosphate pathway is an alternative pathway for glucose metabolism, having a useful role in hydroxylation and anabolic reactions, lipid and steroid biosynthesis and in maintaining the integrity of RBC membranes. After the first step of glycolysis, the PPP branches to generate fructose 6-phosphate (F6P) and glyceraldehyde 3-phosphate (G3P) via oxidative and non-oxidative branches.

It is active in the liver, lactating mammary glands and adipose tissue, generating NADPH [reducing power required for synthesis of fatty acids, sterols, nucleotides and non-essential amino acids, cellular antioxidant defenses] and ribose 5-phosphate (R5P) [building block for nucleic acid synthesis] and is especially active during oxidative stress, e.g. this pathway may become more active in diabetes.

Studies have shown a role for the PPP in obesity-related insulin resistance, insulin secretion and chronic diabetic complications. Obesity-induced inflammation can lead to insulin resistance in the skeletal muscle or liver, resulting in systemic insulin resistance. Macrophages surrounding dead adipocytes cause obesity-induced inflammation and secrete pro-inflammatory cytokines, leading to local insulin resistance. Pro-inflammatory macrophages show enhanced glycolysis and PPP flux, which provide more energy and NADPH to trigger inflammatory responses, secrete pro-inflammatory cytokines and recruit more immune cells. The differential activity of the oxidative PPP in macrophages contributes to this functional discrepancy.

The deficiency of the enzyme glucose-6-phosphate dehydrogenase results in X-linked hemolytic anemia, which is common in persons of Mediterranean descent. Patients with G6PD deficiency show decreased insulin secretion. Thus, the PPP might serve as a promising target for modulating obesity-induced inflammation and insulin sensitivity in different tissues [8].

Glucose Transporters or SWEET Proteins

Glucose transporters (GLUT) are proteins coded by the SLC2 (solute carrier family 2) gene. These aid in the diffusion of substances across the concentration gradient. A total of 14 isoforms have been described, including GLUT1-12, 14 and GLUT 13/HMIT (H+/proton myo-inositol transporter) (Table 7.3) [9].

The proteins usually comprise about 500 amino acid residues with 12 transmembrane spanning alpha helices along with a single oligosaccharide attached at the N terminal. There is a large homology between the GLUT transporters, suggesting a similar process of glucose transport across different tissues. Almost all tissues depend on GLUT receptors for the uptake of glucose. The commonly known isoforms, their location and function are summarised in Table 7.3. GLUT4 is said to be the key insulin responsive form and is expressed in all insulin-sensitive tissues. Expression of some of these GLUT isoforms has been shown to be associated with a poor prognosis, e.g. GLUT and GLU14 in gastric adenocarcinomas.

Table 7.3 The location and substrate specificity of commonly known GLUT transporters

Isoform	Location	Substrate specificity
GLUT1	Placenta, muscle, adipose tissue, brain and endothelium, red blood cells	Glucose, galactose, dehydroacetic acid
GLUT2	Pancreatic beta cells, liver, small intestine and renal proximal tubule, hypothalamus	Glucose, fructose, galactose, glucosamine
GLUT3	neurons, small intestine, testes	Glucose, galactose, dehydroacetic acid
GLUT4	Skeletal muscle, cardiomyocytes, adipose tissue	Glucose, galactose, dehydroacetic acid
GLUT5	Small intestine, brain, muscle and adipose tissue, spermatozoa	Fructose
GLUT6	Brain and spleen	Glucose
GLUT7	Intestine and colon	Fructose, glucose
GLUT8	Testes, brain, fat, liver, spleen	Glucose, fructose
GLUT9	Kidney, liver, placenta, colon	Urate/gluose/fructose
GLUT10	Heart, lung	Glucose
GLUT11	Muscle, heart, placenta, kidney. pancreas, adipose tissue	Glucose
GLUT12	Insulin-sensitive tissues	Glucose/fructose
GLUT13/ HMIT	Brain	Myoionisitol
GLUT14	Testes	Like GLUT 3; it has 95% homology to GLUT 3

In addition to GLUT, specific glucose efflux transporters called the SWEET proteins that help to maintain blood glucose levels are equally important. Glucose efflux from the liver is cardinal in maintaining fasting glucose levels. SWEET1 is expressed in humans as a glucose uniporter and is expressed in the oviduct, epididymis, intestine and beta cell lines.

Organ Systems That Help Regulate Glucose Metabolism

Pancreas

The pancreas plays a critical role in maintaining normal glucose levels both in the fasting and postprandial state. five major hormones secreted by the pancreas help regulate serum glucose levels. Moreover, many of the currently available and upcoming pharmaco-therapeutic agents modulate these hormones in isolation or in combination. The four major cell types in the pancreatic islets of Langerhans that secrete these hormones include the beta cells that secrete insulin and amylin, the alpha cells that secrete glucagon, the delta cells that secrete somatostatin, and the PP cells that secrete pancreatic polypeptide (PPY). The understanding of these hormones is helpful from a clinical standpoint, wherein today the reversal of diabetes is possible through the restoration of pathways mediated by these hormones following significant weight loss [10].

Insulin

Insulin secretion is proportional to serum glucose values. The glucose enters the beta cell via GLUT 2, which in turn stimulates the insulin release via K-ATP dependent and independent channels. Postprandial insulin secretion occurs in two phases. The first phase is essentially the release of the preformed insulin, followed by a gradual release during the second phase. Following insulin secretion, glucose regulation occurs at several sites. These include reducing hepatic gluconeogenesis and glycogenolysis, enhancing glycogenesis in the liver and muscle, increasing glucose uptake in the adipose tissue and muscles and also increasing the expression of glucose transports like GLUT1 and GLUT4 in non-hepatic tissues.

Glucagon

Glucagon is a hormone secreted in response to hypoglycemia. Its secretion is activated by the generation of the activation of sodium and calcium ion action potentials stimulated by low blood glucose. It primarily acts on the liver by stimulating glycogenolysis and gluconeogenesis. It also reduces glycogenesis and glycolysis. Glucagon also enhances amino acid uptake in the liver, coupled with enhanced glycerol production by adipose tissue, thereby providing an adequate substrate for gluconeogenesis.

Somatostatin

Somatostatin is known to be produced by several organs, including the delta cells of the pancreas, the intestinal tract and even the central nervous system. Though it has no direct effect on glucose production, its release causes a potent paracrine local inhibitory effect on surrounding alpha and beta cells. The insulin and glucagon levels measured in the portal vein are significantly reduced following somatostatin infusion. The glucose stimulated release of somatostatin is mediated through the calcium channels.

Amylin

Amylin is stored in secretory granules and co-secreted with insulin by the beta cells in response to glucose, akin to insulin. However, it is secreted in a ten-fold lower molar ratio than insulin. Plasma amylin levels increase in the postprandial/postglucose administration and are directly proportional to body fat percentage. Amylin facilitates the inhibition of postprandial glucagon secretion and retards gastric emptying. It is also implicated in improving satiety. Amylin analouges have been used in the treatment of diabetes, but more recent molecules like cagrilinitide have shown to be very effective in the management of obesity [11].

Pancreatic Polypeptide

The pancreatic polypeptide is secreted by the F cells, which are also called the PP cells, and requires an intact vagus nerve for secretion. Like amylin, the pancreatic polypeptide increases following the ingestion of food in a dose-dependent manner. It reduces fatty acid levels and inhibits other pancreatic hormone secretion.

Liver

The liver is regarded as the key organ for glucose metabolism. The glucose uptake in the hepatocytes occurs with the help of GLUT-2 receptors. This glucose is further phosphorylated by the enzyme glucokinase to glucose-6-phosphate, which in turn is further directed to glycogenesis, the pentose phosphate pathway, or glycolysis. This helps the liver maintain glucose homeostasis.

Following glucose intake and subsequent hyperglycaemia along with hyperinsulinemia, the liver homeostasis shifts from a fasting state to a state of storage. Both glycogenolysis and gluconeogenesis are temporarily halted for up to 6 hours, the former more than the latter.

Moreover, up to 90% of all the glucose in the circulation that is not derived from diet is produced by the liver. Following prolonged fasting, exercise or hypoglycemia, glycogenolysis sets in. Furthermore, the gluconeogenic enzymes, namely, phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, are activated. These are promoted by glucagon, cortisol and the interleukin-6 family of cytokines and inhibited by insulin. Glucagon also facilitates the inhibi-

tion of hepatic glucose by the liver to further conserve the low amount of available glucose during these times. The skeletal muscle also facilitates the release of lactate, which can be shuttled back to the liver (Cori's cycle).

Kidney

After the liver, the kidney is regarded as the next key regulator of glucose in the body. It is responsible for the release of glucose into the circulation following gluconeogenesis, the uptake of glucose from the circulation and also reabsorption of the glucose from the glomerular filtrate. However, kidney is unable to produce glucose through glycogenolysis. Gluconeogenesis occurs in the renal cortex and is primarily regulated by insulin and adrenaline. The key substrates used for this are lactate, glutamine and glycerol. The renal medulla helps in glucose utilisation. Following an overnight fast, about 25% of the glucose released in the circulation is derived from the kidneys. Insulin facilitates renal glucose uptake, reduces renal gluconeogenesis and also decreases the available substrates for gluconeogenesis. On the contrary, adrenaline, stimulates renal gluconeogenesis and reduces renal glucose uptake. Glucagon has only been shown to act on the kidneys in animal studies.

Glucose reabsorption from the glomerular filtrate is also very important. With a normal glomerular filtration rate of 180 mL, approximately 160 g of glucose is reabsorbed in a normal individual. This is primarily mediated by the sodium glucose transporters (SGLT) present in the proximal renal tubule. Ninety percent of this is reabsorbed by the SGLT-type 2 receptor, which is present in the convoluted section of the proximal tubule, and the remaining 10% is absorbed by the SGLT-1 receptor, which is present in the straight section of the proximal tubule.

Role of the Hypothalamic Pituitary Axis

The regulation of food intake and energy homeostasis is regulated by the cross talk between the brain and the gastrointestinal system. Though several areas of the brain are responsible for this regulation, the key region is the hypothalamus, which in turn can regulate the autonomic nervous system (ANS). The ANS is helpful for the regulation of insulin and glucagon secretion and also the metabolic activity of the liver, muscle and adipose tissue [12]. This regulation is mediated through a direct effect on the autonomic nerves innervating the pancreas as well as indirectly by altering the catecholamines through the adrenal medulla. The feedback loop is completed by the signals received by the hypothalamus for the various hormones summarised in Fig. 7.3 [13].

The regulation through the hypothalamic pituitary adrenal axis is mediated by corticotrophin-releasing hormone (CRH) production, which further regulates adrenocorticotropic hormone (ACTH) and cortisol production. This has a major impact on glucose metabolism. Cortisol activates glycogen synthase as well as inhibits the phosphorylation of glucose, overall increasing the glycogen synthesis. Glucocorticoids also lead to lipolysis in the adipose tissue and proteolysis in the muscles, resulting in the release of glycerol and amino acids, respectively. These act as substrates for gluconeogenesis. Cortisol also inhibits the actions of insulin at the level of the liver and muscles and thereby stimulates gluconeogenesis at the liver. It also acts at the level of the beta cells to reduce the secretion of insulin. The regulation of the hypothalamus through the hypothalamic-pituitary-thyroid axis is also an important channel to modulate glucose homeostasis. T3 regulates the gene expression of enzymes responsible for glucose and fatty acid oxidation, glycolysis and cholesterol biosynthesis. T3 also directly stimulates basal and insulin medicated glucose uptake in the skeletal muscle through enhanced GLUT-4 expression.

Human Growth Hormone secretion is regulated through the hypothalamic hormones, namely, the Growth hormone–releasing hormone (GHRH) and somatostatin, which also antagonise insulin action, increase the fasting hepatic glucose output and decrease the peripheral glucose utilisation. GnRH-mediated estrogen regulation, is another way the hypothalamus is able to regulate glucose homeostasis. Estrogen enhances insulin action and increases the peripheral expression of glucose transporters. Similarly, testosterone in hypogonadal men helps to reduce insulin levels and improve the capacity of the muscle to enhance glucose uptake.

Gut Regulation of Glucose: Role of Incretin Hormones

The exaggerated insulin release following oral glucose ingestion as compared to intravenous glucose infusion, known as the incretin effect, suggested the vital role of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), in the regulation of blood glucose. While GIP is more potent, GLP-1 is secreted in greater quantities and has gained more recognition in humans [14].

GIP, secreted by the K cells in the duodenum, helps in the stimulation of insulin release and regulates fat metabolism. GLP-1, which is secreted by the L cells in the ileum and colon, also helps in inhibiting glucagon secretion and delaying gastric emptying. The regulation of glucose by GLP-1 is only mediated in the postprandial state in a glucose-dependent manner and not when glucose levels are in the normal or hypoglycaemic range. While GLP-1 blunts the glucagon response in the postprandial state, it does not alter its secretion during an episode of hypoglycemia. The impact of GLP-1 on gastric emptying and gastric acid secretion, is driven by its central actions mediated by the vagus nerve. The plasma half-life of GLP-1 is about 2 minutes, as it is rapidly degraded by the enzyme dipeptidyl peptidase-IV

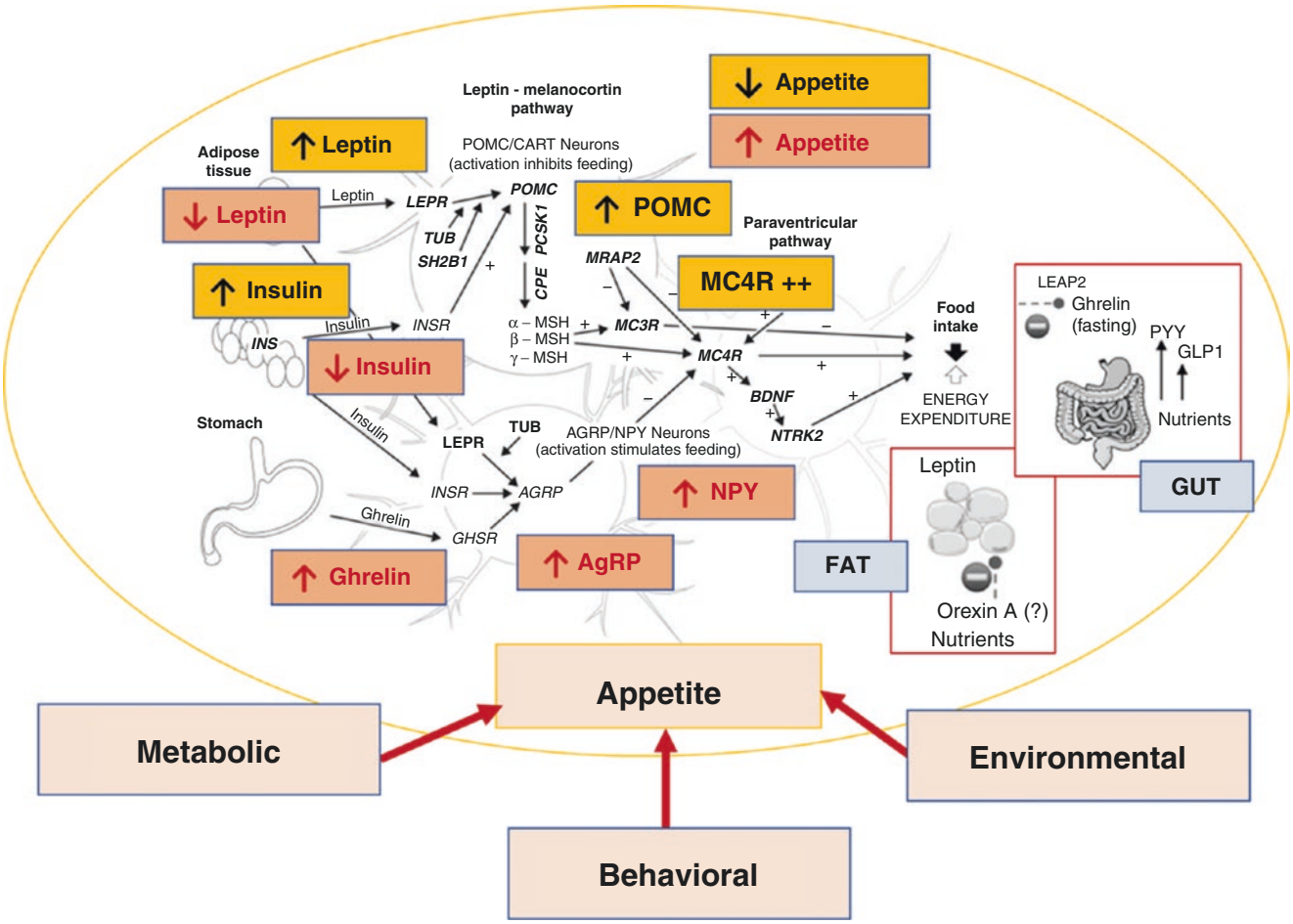

Fig. 7.3 Pathways responsible for the regulation of appetite in the hypothalamus, *AgRP* agouti-related protein; *PYY* peptide YY; *MC4R* melanocortin 4 receptor; *POMC* proopiomelanocortin; *LEAP2* liver-expressed antimicrobial peptide 2; *GLP1* glucagon-like peptide-1

(DPP-IV). GLP-1 levels are significantly reduced in people with prediabetes and established type 2 diabetes mellitus. GLP-1 analogues and DPP4 inhibitors have been used for the management of obesity and diabetes, in clinical practice. There is also an emerging interest in studying the role of GLP-1 in the preservation of beta cell function and proliferation.

Gall Bladder: The New Metabolic Orchestrator

More recently, the gall bladder has been identified as an important regulator of metabolic parameters. This initially emerged from data in patients after cholecystectomy, wherein it was found that the odds ratio of having type 2 diabetes after cholecystectomy increased several fold as compared to those not undergoing cholecystectomy. Though the long-known function of the gall bladder is to store, concentrate and release bile into the gut, more recently it has been described as an endocrine organ. The intermittent release of bile acids and FGF-19 into the circulation through the bile has been shown to have a positive impact on the metabolic profile of a given individual. The loss of this function following cholecystectomy has been implicated in the metabolic disturbances in these patients. FGF-19 is secreted from the gall bladder mucosa into the bile and helps to reduce serum triglycerides, cholesterol and promote glycogen synthesis. FGF-19 has also been shown to suppress insulin-induced fatty acid synthesis in the liver. Large pulses of bile acids in the postprandial state help to increase GLP-1 mediated insulin secretion, reduce gluconeogenesis through FGF receptor 4 (FGFR4) and increase glycogenesis and reduce glycogenolysis through the Farnesoid-X-Receptor (FXR). Though this is still an active area of research, this may have implications for monitoring individuals post cholecystectomy.

Key Summary Points

1. Glucose homeostasis with the interplay of various hormones is imperative to maintain blood glucose levels in a narrow "normal" range.
2. The five phases of glucose homeostasis reflect the different fed and fasting states, and the consequent change in the metabolic pathways helps the human body to adapt to these states.
3. The main carbohydrate pathways for glucose homeostasis are as follows:
   (a) Carbohydrate digestion (in the intestine)
   (b) Fructose metabolism (in the liver)
   (c) Galactose metabolism (in the liver)
   (d) Glucose oxidation via glycolysis (in the cytoplasm), oxidative decarboxylation reaction (in the mitochondria), citric acid cycle (in the mitochondria) and the electron transport chain (ETC) (in the mitochondrial intermembrane space)
   (e) Glycogenesis (in the liver and skeletal muscle)
   (f) Glycogenolysis (in the liver, skeletal muscle and kidney)
   (g) Pentose phosphate pathway (in the liver, adipose tissue, adrenal cortex, testis, milk glands, phagocyte cells and red blood cells (RBCs))
   (h) Gluconeogenesis (in the liver, kidney, brain, testes and erythrocytes)
4. The transport of glucose across cell membranes is carried out by a family of structurally related proteins known as glucose transporters. Glucose transporters broadly have been classified into three types: GLUTs, SGLTs and the recently discovered, SWEET transporters.
5. Several organ systems play an important role in glucose metabolism. These include the pancreas, liver, kidney, brain, hypothalamus and gastrointestinal tract. Gall bladder is newly added to this list. The understanding of these physiological processes improves the clinician's understanding in diseased states as well as helps to explore novel therapeutic targets to manage disorders of glucose homeostasis.

Multiple-Choice Questions

1. With reference to the regulation of the internal environment, the term "homeostasis" was coined by
   (a) **Walter B. Cannon**
   (b) Claude Bernard
   (c) Linus Pauling
   (d) Joseph Barcroft
2. The molecule at the centre of various metabolic pathways of glucose homeostasis is
   (a) Glucose
   (b) Fructose-6-phosphate
   (c) **Glucose-6-phosphate**
   (d) Ribose-5-phosphate
3. In which phase of glucose homeostasis, the ketone bodies may become the major fuel for the brain?
   (a) Phase 7
   (b) **Phase 5**
   (c) Phase 3
   (d) Phase 1
4. Which of the following is a key metabolic process in the "fed state"?
   (a) Glycogenolysis
   (b) Lipolysis
   (c) **Glycolysis**
   (d) Gluconeogenesis
5. Deficiency of the enzyme glucose-6-phosphate dehydrogenase results in X-linked hemolytic anemia. These patients with G6PD deficiency may show which of the following abnormalities affecting homeostasis?
   (a) **Decreased insulin secretion**
   (b) Decreased ketone body formation
   (c) Decreased lipolysis
   (d) Decreased protein catabolism
6. All of the following Glucose transporters help in the transfer of glucose, except
   (a) GLUT 11
   (b) GLUT 12
   (c) **GLUT 13**
   (d) GLUT 14
7. All are true about SWEET proteins, except
   (a) **SWEET1 is not expressed in humans**.
   (b) It is a glucose uniporter.
   (c) It is expressed in the oviduct, epididymis and intestine.
   (d) Aids in glucose efflux

8. All of the following hormones are secreted by the pancreas, except
   (a) Amylin
   (b) Pancreatic polypeptide
   (c) **Glucagon Like Peptide—1**
   (d) Somatostatin
9. Activation of all of the following reduces calorie intake, except
   (a) MC4R
   (b) POMC
   (c) Leptin
   (d) **NPY**
10. Glucose regulation by the gall Bladder is mediated by all of the following, except
   (a) Intermittent release of bile acids
   (b) Production of FGF-19
   (c) GLP-1 mediated insulin release
   (d) **Increased production of adiponectin**

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Pathophysiology of Type 1 Diabetes

8

Rita Gomez-Diaz

Abbreviations

Anti-GAD	Antibodies against glutamic acid decarboxylase
Anti-IA2	Anti-tyrosine
CRTAM	Class I restricted T cell-associated molecule
CTLA-4	Cytotoxic T-lymphocyte antigen
CTSL	Cathepsin-L lysosomal protease
IA2	Insulinoma antigen 2
ICOS	Inducible gene costimulatory molecule
IFIH1	Induced interferon with dominion 1 helicase C
IFN-δ	Interferon gamma
IL2RA	Interleukin 2 receptor alpha chain
ISGs	Interferon-stimulated genes
MHC	Major histocompatibility complex
NKT	Natural killer lymphocyte-type
NOD	Nonobese diabetic mouse models
PTPN22	Protein tyrosine phosphatase, non-receptor type 22
T1D	Type 1 diabetes
TCR	Receptor for T lymphocyte antigen
WHO	World Health Organization
ZnT8	Zinc cation transporter

Introduction

Type 1 diabetes (T1D) is a chronic disease measured by immunity with a silent period that lasts for a varied time before clinically manifesting, characterized by selective loss of insulin-producing cells in the pancreatic islets of genetically susceptible individuals. It is known that the pathogenesis of this disease occurs in stages, with variations among individuals who have different genetic susceptibilities. The environmental factors may come into play as early as during gestation and would continue through early childhood. Immune dysregulation leads to beta cell destruction long before classical autoantibodies are detected. The C-peptide response is diminished at least 2 years before disease diagnosis [1]. In the last 10 years, new knowledge has been added to both the pathogenesis and treatment of this disease. The search is ongoing for new tools that can identify the earliest stages of autoimmune activation in type 1 diabetes. A better understanding of the physiopathology of this disease can change the approach to treatment and prevention.

Etiopathogenesis of Type 1 Diabetes

There is evidence that type 1 diabetes is considered an organ-specific autoimmune disease in which genetic factors (such as a strong association with HLA haplotypes and genetic linkage with immune system genes), immunological factors (such as specificity for beta cells and the presence of antigen-specific T cells), environmental factors (such as age at onset), and gut microbiota participate. It is also known that type 1 diabetes onset is triggered by an inappropriate activation of both the innate and adaptive immune systems, which causes a cascade that results in pancreatic islet destruction. Invariant natural killer T (NKT) cells interact with both systems and serve as a junction between them. Since they function through the production of cytokines, it has been suggested that they would be intrinsically involved in the disease. Figure 8.1 shows the pathogenesis of type 1 diabetes. The upper portion shows the various stages, as described by Eisenbarth [1]. Stage 1 involves genetic susceptibility. In stage II, an environmental factor triggers the immune process. During stage III, beta cell antibodies and active self-autoimmunity are present. In stage IV, metabolic abnormalities appear, leading to the symptoms manifested in stage V. Finally, in stage VI, insulin dependency results. The lower portion of the figure shows the participation of $CD4^+$, $CD8^+$, and NKT cells in the onset of T1D.

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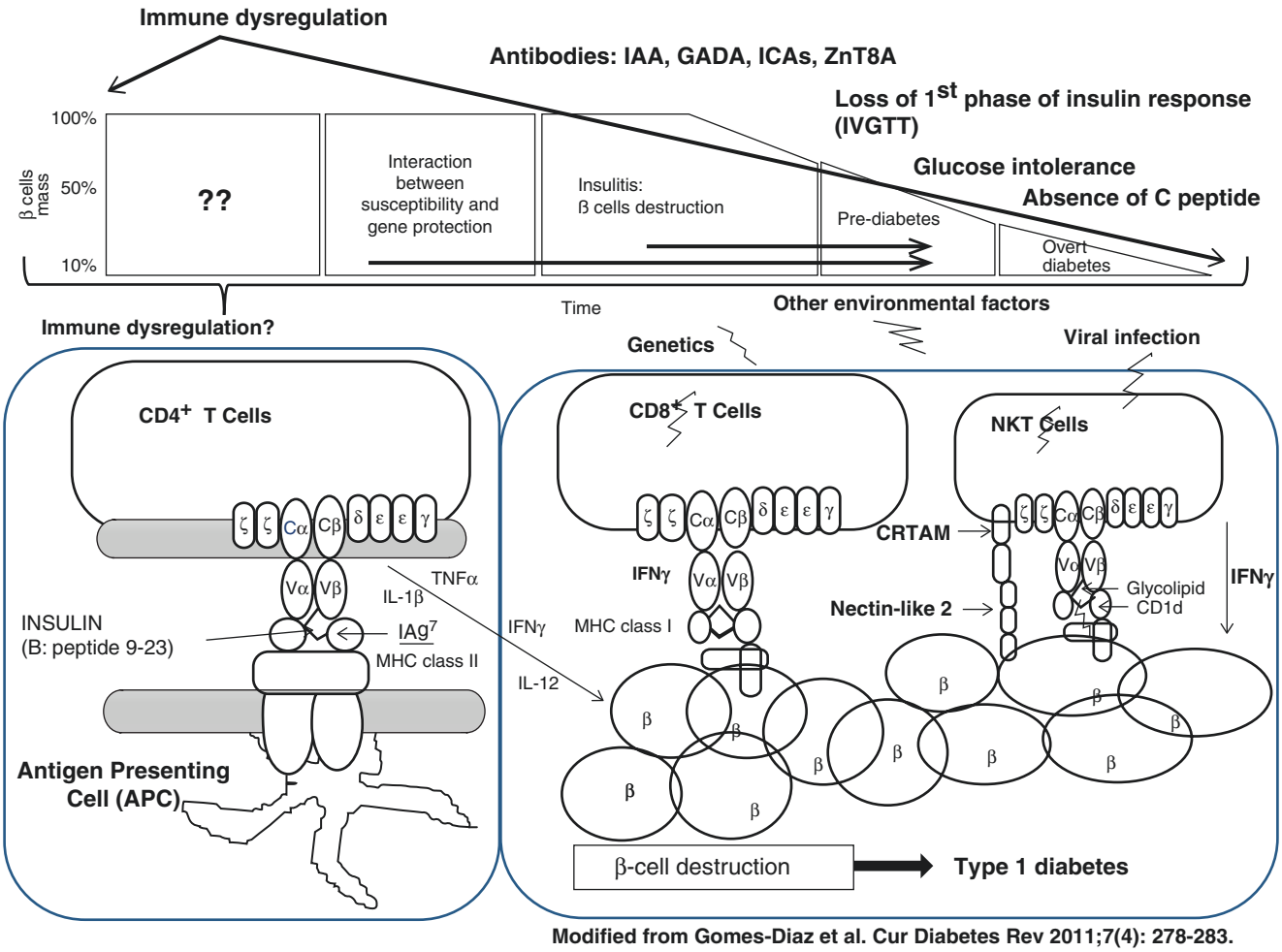

Fig. 8.1 Pathogenesis of type 1 diabetes. (Modified from Gomez-Diaz et al. Curr Diabetes Rev 2011;7(4):278-283)

The role of NKT cells in the physiopathology of type 1 diabetes will be discussed below.

Genetic Factors

The family histories observed in epidemiological studies have sustained the search for genetic causes of T1D. The major histocompatibility complex (MHC) holds a unique position as the link that unites clinical, immunological, and genetic medicine; many diseases, including T1D, have been associated with genes located in the MHC. The most important genes are coded for the group of leukocyte antigens (HLA), a family of surface proteins essential for immunological function. HLA genes present a great variety that has given rise to diversity in immune response and susceptibility to various diseases. Overexpression of HLA molecules is considered a principal characteristic of type 1 diabetes pathogenesis and earmarks a chronic inflammatory state.

The HLA molecules associated with T1D are class II and are coded in the short arm of chromosome 6p21 (IDDM1) [2, 3]; they are responsible for the selection in the thymus of the repertory of T cells and participate directly in the presentation of antigens in the T CD4+ cells. The genetic region of class II HLA contains alleles DP, DQ, and DR, which in turn are divided into subregions.

The genes of the HLA system are the most important in conferring protection or susceptibility for type 1 diabetes, and it is believed they contribute to between 30% and 50% of the risk in the development of the disease. There are two combinations of HLA genes (or haplotypes): HLADR3-DQ2/DR4-DQ8 have a 20 times greater risk of developing type 1 diabetes compared with the general population and are present in 90% of the children with type 1 diabetes. A third protector haplotype, DR15-DQ6, is found in less than 1% of children with T1D and 20% of the general population. The genotype that combines the two susceptibility haplotypes (DR4-DQ8/DR3-DQ2) increases the risk of contracting the disease and is most frequent in children that present at an

early age [4]. It has been suggested that, in the presence of these haplotypes, the first signs of beta-cell autoimmunity might appear as early as during the first year of life [5]. Likewise, protection alleles have been reported in the Caucasian population as being DRB1-DQB1 DRB1*1602-DQB1*0602, DRB1*07-DQB1*0303, DRB1*13-DQB1*0603, and DRB1*14-DQB1*0503 [6]. First-degree relatives with positive antibodies but protector alleles delay or nullify their debut, which might indicate that the protector effect exerted by these genes occurs after the immunological process has begun.

On the other hand, the DIAMOND Project of the World Health Organization (WHO) tested the hypothesis that the variation in the expression of some risk genes for type 1 diabetes influenced the incidence of the disease according to the participating country (mainly alleles DQA1 and DQB1 with sequence codes for arginine in position 52 of the alpha chain for DQ and another amino acid apart from aspartic acid in position 57 in the beta chain of DQ, respectively). Mexico was included among the countries reporting a low incidence at the time of the study, being that DQA1*0301 was the only allele consistently associated with type 1 diabetes [7].

In the Mexican-American population, DRB1*0302 is a risk allele, while the protector is DRB1*1402. In contrast, in Mexican Mestizos, the protection haplotype is DR5/DQ6 (DRB1*0501, DQA1*0102, DQB1*0602), and for risk, it is DR4/DQ8 (DRB1*0405, DQA1*0301, DQB1*0302) [8–10]. However, the fact that 38% of the population has DR3 or DR4 indicates that there must be other factors. Effectively, it has been observed that 95% of the DR4 that have allele DQB1*0302 have diabetes, while the DR4/DQB1*0301 do not. These data suggest that HLA DQ molecules are more important in susceptibility to diabetes, and the association with DR is due to the linkage disequilibrium (association between alleles) that exists between HLA DR and HLA DQ genes [11, 12].

In addition, evidence of the participation of class II HLA in physiopathology has been observed in the murine model, since these molecules participate in the tri-molecular complex that involves a peptide and the T cell receptor of autoreactive cells that escape from the thymus. One of the peptides recognized is the I-Ag-7 molecule (part of the insulin B chain) [13]. This molecule may be involved in epigenetic alterations in Tregs of CD4+ T cells in humans [14].

Nevertheless, even when the association of HLA alleles and haplotypes is strong, these loci represent less than 50% of the genetic contribution to susceptibility to the disease; this is due to the fact that the alleles are not totally penetrating, implying that not all who have inherited them develop the disease. This has pushed T1D research to new immunological and genetic horizons, such as nonclassical HLA proteins including HLA-E, HLA-F, and HLA-G [15].

The other 50% of susceptibility to developing type 1 diabetes is given by non-HLA genes. Genomic association studies have identified around 40 non-HLA polymorphisms and other candidate loci in population studies. One of the most important is a polymorphism in the region of the insulin promotor gene, in chromosome 11p15.5 (locus IDDM2, polymorphism that consists in the number of tandem repetitions: VNTR) [16–19]. The insulin gene is transcribed and translated into the thymus and regulates glucose metabolism through insulin tolerance.

Many other susceptibility loci have been proposed after genome scanning (IDDM3-15). Another of the non-HLA genes that has been associated with T1D is the gene located in chromosome 1p13: protein tyrosine phosphatase, non-receptor type 22 (PTPN22). PTPN22 codes a specific lymphocyte phosphatase that inhibits T cell activity; the variant that changes arginine for tryptophan in position 620 alters the B and T cell response, which is accompanied by a reduction in T cell inhibition, promoting multi-organic autoimmunity, but the specific genes responsible have not yet been identified [20–22].

The genetic evidence for the participation of peripheral B cell compartments and production of cytokines (IL-10) was measured by flow cytometry by Thompson et al., who did not find evidence of changes in IL-10 production through in vitro stimulation with IL-21, suggesting that the pathogenetic role of the B cells is limited to the early stages of the disease in the isles of Langerhans and in the draining pancreatic lymph nodes [23].

IDDM12, located on chromosome 2q33, is one of the confirmed susceptibility loci for T1D [24]. This 300-kilobase region contains at least 3 genes: CD28, cytotoxic T-lymphocyte antigen (CTLA-4: cytotoxic T-lymphocyte associated protein A), and the inducible gene costimulatory molecule (ICOS). CTLA-4 codifies a molecule that is expressed on the surface of activated T cells, so polymorphism A49G has been associated with a reduction in the activation and proliferation of T cells. Genetic mapping has suggested that CTLA-4 or a closely related gene may be implicated in susceptibility to type 1 diabetes [25]. Other non-HLA risk genes include the interleukin 2 receptor alpha chain (IL2RA) as well as induced interferon with dominion 1 helicase C (IFIH1) [26, 27]. However, it was recently found that there was a significant association between the non-HLA risk genes and positivity for autoimmune antibodies. For example, PTPN22 associates with anti-GAD autoantibody, while ERBB3 associates with anti-IA-2 antibody ($p = 0.042$). By the same token, IL2RA and INS-VNTR associate with anti-insulin antibodies [28].

Other non-HLA genes not yet linked with specific antibody positivity include TFPR3, which mediates the release of intracellular calcium; BACH2, which coordinates the activation and repression of MAFK; and UBASH3A, which

promotes the accumulation of target receptors, including T cell receptors [29].

Taking all of this into account, it has been proposed that a combination of HLA and non-HLA genetic risk scores could prove to be a predictor of T1D risk [30]. This concept is further supported by a recent study which found an area under the curve for a non-HLA genetic risk score of 0.56, and for HLA, the area under the curve was 0.78 [31].

Immunological Factors

Very little has been definitively proven concerning the immunological factors involved in T1D. But as noted by Mannering et al., "an absence of evidence should not be confused with evidence of absence" [32]. To date, the known participation of the autoimmune component comes from various kinds of evidence. Insulitis is defined as an inflammation of the islets of Langerhans that results in the destruction of insulin-producing beta cells. Primary damage is due to an immune response mediated by cells, where Th1 cells (CD4+) collaborate during activation of specific in situ Tc cells (CD8+, associated with Th2) and are directed against the beta cell.

Thus, a chronic autoimmune response is manifested clinically with the destruction of 60–80% of pancreatic β insulin-producing cells [33]. The insulitis observed in the islets, as well as their surroundings, is constituted mainly of macrophages, B and T lymphocytes [34], and dendritic cells. Various studies have shown that inflammation appears in stages prior to the manifestation of tissue damage, and the destruction of beta cells activates the dendritic cells, which trigger the T cells in the pancreas [35].

Insulitis is diagnosed with the presence of at least 15 CD45+ cells per islet, in at least 3 islets. Long considered the pathologic characteristic of type 1 diabetes, it is usually, but not always, detected together with insulin-positive beta cells [36].

Although normally associated with younger patients, it has been suggested that this association is overestimated. Nevertheless, the presence of insulitis has been found in a majority of recent-onset type 1 diabetes patients [37]. However, the presence of insulitis has been shown to have an inverse correlation with time with diabetes, but not with age at onset [36]. Insulitis is probably the main cause of the destruction of T γδ lymphocytes even after 1 year of insulin treatment, which might explain part of the evolution of the disease [38].

It was recently found that islet-invading T cells differ from allogeneic T cells. There are even differences between type 1 diabetes patients and patients with allograft rejection. Those with diabetes show very low levels of cytokines and chemokines [37].

Interferon-stimulated genes (ISGs) are up-regulated by interferon to put cells into an anti-viral state. These include GBP1, TLR3, OAS1, EIF2AK2, HLA-E, IFI6, and STAT1. In type 1 diabetes and/or insulitis, the levels of these genes are increased. The presence of insulitis in the peri-islet area has been found to increase the levels of ISGs up to fivefold. However, the actual role of this overexpression in the progression of type 1 diabetes remains to be clarified [39].

Nevertheless, there are differences in youth and adult onset of T1D. In youth, there is a rapid loss of beta cells (75–85%), offset by a high potential for beta cell regeneration. The autoantibodies presented are mainly anti-insulin. In contrast, in adult-onset T1D, the loss of beta cells is more gradual (60–75%), but with a lower possibility for regeneration. There are more anti-GAD antibodies. The loss of C-peptide production varies greatly, and the reasons are not yet understood [40].

There is a direct correlation with the presence of T lymphocytes producing interferon gamma (IFN-δ) in the infiltrates located in the islets [41–45]. In fact, Gomez-Tourino et al. indicate that CD4 T cells can be considered to be characterized by the secretion of either IFN-δ or IL-17, as opposed to the secretion of IL-10 in healthy subjects. They support the important role that T1 (IFN-δ) and T17 (IL-17) play in the development of type 1 diabetes [46]. On the other hand, Mannering et al. not only showed that $CD4^+$ T cells are associated with HLA risk genotypes for T1D but also noted that clones of these T cells could recognize epitopes from the proinsulin C-peptide [32, 47].

A secondary effect is that specific autoantibodies are produced against auto-antigens of the pancreatic islets. The quantification of antibodies against auto-antigens has been useful in knowing the activity of the disease, determining its degree of progression, and contributing to the classification and prediction of the clinical status of the patients. From 60 to 80% of patients recently diagnosed present antibodies against glutamic acid decarboxylase (anti-GAD); a similar percentage (60–70%) show anti-tyrosine (anti-IA2) of zinc cation transporter (ZnT8), and only 30–50% have anti-insulin antibodies [48–50]. Nevertheless, the sensitivity and specificity of these autoantibodies vary with ethnicity and with follow-up time. However, as shown by Velluzzi et al., while positivity for 1 of these antibodies has a hazard ratio of 55.3, this drops to 14.5 with 2 positive antibodies and 3.0 for 3 [51].

In this regard, $CD8^+$ T cells have been suggested as the final cause of beta cell death. This has been supported by the presence of antigen-specific (GAD65) and HLA-restricted forms. $CD8^+$ T cells can be specific for various epitopes,

including insulin, insulinoma antigen 2 (IA 2), and GAD-65, and are pathogenic to beta cells [47]. Another study has suggested that $CD8^+$ T cells are autoreactive against such autoantigens as GAD65, ZnT8, and IA-2 [32, 38].

Environmental Factors

The rapid increase in the prevalence of type 1 diabetes, both in our country and worldwide, cannot be explained solely by the genetic component (in subjects with risk HLA haplotypes). Epigenetics is considered a nongenetic factor that possibly involves cells of both innate and adaptive immune responses, causing alterations in DNA methylation [52]. Epigenetic modifications are those that may be key regarding environmental risk factors and are probably in line with the hygiene hypothesis, which proposes that environmental exposure to microbes and other pathogens and their subproducts early in life induces immunological tolerance and a reduction in atopy and autoimmune diseases.

Recently Singh et al. noted the epigenetic changes in T1D, such as the interaction between DNA methylation and the modification of histones and variants in the helicase C domain 1 (IFIH1) gene [53].

Said changes between the genetic and environmental factors may lie in IFIH1, also known as MDA5, or the gene associated with differentiation of melanoma 5, detection of intracellular RNA of the picornavirus, a virus family that includes enterovirus. Detection of intracellular RNA leads to the activation of IFIH1 and the interferon route. It has been hypothesized that enteroviruses lead to the activation of IFIH1 in the β cells of the pancreas, elevated interferon levels, an increase in MHC class I expression, activating CD8 T cells, and the death of pancreatic β cells. The variants that result from less function of IFIH1 are protectors from type 1 diabetes [32].

Some other viruses [54] (*Coxsackie B*, *parotitis* [55], and rubella [56]) have been implicated as possible initiators, accelerators, or precipitators of the disease. The virus with the most demonstrated role is congenital rubella syndrome (children that acquire the infection in utero), where there is a 30% risk of presenting type 1 diabetes between 5 and 30 years later; however, this only explains a small proportion of the cases.

Many of the viruses use different mechanisms to ultimately lead to beta cell death. In the case of the rubella virus, it causes two-way reactions between the antigens and GAD, stimulating T lymphocyte activity and leading to beta cell infection. Cytomegalovirus also causes infection of beta cells but uses clonal activation of T cells to induce the recruitment of macrophages to the pancreas. However, in the case of mumps, there is increased expression of class I and II HLA in the beta cells, while rotavirus uses molecular imitation to infect the cells. In contrast, parvovirus does not infect beta cells, but rather uses macrophages to activate a ThI immune response while at the same time increasing Th2 responses [57].

It has been suggested that the inability to quickly cure viral infections could be part of the reason that beta cells, but not alpha cells, suffer apoptosis during the development and progression of type 1 diabetes [58]. The "bystander hypothesis" infers that the infection of pancreatic cells leads to the release of pro-inflammatory cytokines, which may explain the aforementioned cell death [59, 60]. However, the "molecular mimicry" mechanism attributed to rotavirus, among others, remains controversial, due to conflicting experimental results [59, 61].

In fact, infection may delay or avoid the development of type 1 diabetes through various mechanisms. Over time, there is a mutual adaptation. Infections which trigger immunoregulatory cytokines, such as IL-10, help control inflammation and also reinforce regulatory T cell activity while sparking NKT cell activity. On the other hand, activated macrophages and "tolerogenic" dendritic cells inhibit Th1 responses through a variety of mechanisms, such as rerouting the response to Th2, prompting T cells, and producing amino acid catabolizing enzymes. This activity limits tissue pathology [62].

Nevertheless, the enterovirus genus has been given special attention in regard to type 1 diabetes, thanks to advances in techniques to identify it. Enteroviruses are the most common viruses causing disease in humans, including foot-and-mouth disease and poliomyelitis. Most are extremely resistant to antibiotics, as well as to the chlorine usually added to treated water, meaning they can be transmitted by water, food, or soil. This genus includes the *Coxsackie* family, most notoriously *Coxsackie B*. One study found enteroviral genomes in the islets in pancreatic biopsies of patients with type 1 diabetes [63]. In the Diabetes Virus Detection Study (DiViD), enterovirus was found in all of the insulin-containing islets of pancreas samples of patients with recent-onset (<10 weeks) type 1 diabetes [64]. This supports the idea that viral infection precedes the appearance of diabetes. Several other studies in children have reached the same conclusions, such as VirDiab [65] and the study conducted by Laitinen et al. [66], both of which were carried out in children with type 1 diabetes against apparently healthy controls. With the growing body of evidence, it has been suggested that the enterovirus infection, and possibly other viral infections as well, may be the last straw and push an already unbalanced metabolism into a critical loss of beta cells [67]. Nevertheless, for the virus to have an effect, it has

been suggested that a second factor should also be present, such as a genetic or epigenetic predisposition [68].

On the other hand, among the environmental risk factors studied is diet, especially during the lactation period, which can modulate intestinal microbiota and is among the mechanisms that influence type 1 diabetes. Various studies have considered early exposure to cow's milk and highly hydrolyzed casein formula as the trigger for autoimmunity in some genetically susceptible individuals [69–72]. However, studies of the association between vitamin D, another suspected factor, and the development of type 1 diabetes remain controversial [73, 74]. Nevertheless, a recent study has found a significant inverse relationship between vitamin D and C-reactive protein, as well as with various cytokines, including IFN-γ, TNF-α, IL-6, IL-1β, IL-4, and IL-10 [75].

Microbiota

The development of intestinal microbiota is influenced by many factors, including diet, lifestyle, use of antibiotics, type of birth (natural or cesarian), and breastfeeding. It is known that a balance in the intestinal microbiota is fundamental for a wide variety of physiological mechanisms, including the function of the immune system. It has been suggested that an imbalance in the intestinal microbiome, called dysbiosis, is related to the pathogenesis of type 1 diabetes.

In genetically susceptible subjects, the intestinal microbiota plays a decisive role in the maturity of the immune system. Intestinal dysbiosis can interrupt the integrity of the intestinal barrier, allowing the unregulated passage of antigens that escape from antigen-presenting cells (APC), bringing deregulation of the immune response, including the innate and adaptive immune systems, resulting in the destruction of beta cells and the appearance of T1D [76]; therefore, immune maturity mediated by intestinal microbiomes during the first 3 years of life is fundamental to prevent the development of disease [77]. It was recently reported that high levels of *Firmicutes* confer 7.3 (CI: 2.2–23.5) times more risk of type 1 diabetes, while a higher number of *Bifidobacterium* in the intestine was a protector factor (1.03, CI: 1.01–1.05) [78].

In light of these facts, several recent studies have examined the microbiome profiles of healthy individuals compared with those with T1D. One such study, conducted in Spain, found significant differences between *Bifidobacterium, Lactobacillus*, and *Clostridium.* Patients had higher levels of *Clostridium* and lower levels of *Bifidobacterium* than controls, suggesting a relationship with glycemic levels. In addition, they found that the quality of the bacteria was lower in T1D children than in healthy controls [79]. This agreed with a later study, also in Spain, which found higher *Clostridium*, *Bacteroides*, and *Vellionella* and lower *Bifidobacterium* and *Lactobacillus* in T1D patients [80]. This contrasts with a study in the Netherlands, which found higher levels of *Bacteroidetes* and lower levels of *Clostridium* (IV and XIVa) in T1D, which was found to be age-specific (2.9 years) [81]. Another study in Mexican children in Sonora found that newly diagnosed cases of T1D showed high levels of *Bacteroides*, while healthy children had high levels of *Prevotella*. However, after 2 years of treatment, the levels of both bacteria had returned to those of the healthy children, suggesting not only the involvement of dietary changes but also the possibility of using therapies with microbiota to reduce the possibility of developing diabetes [82].

The development of gut microbiota is influenced by changes in diet, which may explain the influence of breastfeeding and the introduction of solid food [83].

Nevertheless, whereas children with T1D have high levels of *Bacteroidetes*, children with obesity have reduced levels but increased *Lactobacillus*, which indicates an important difference in the two conditions [82, 84]. However, this difference may depend on other factors, such as genetic risk, in addition to the gut microbiota profile. In a portion of the TEDDY study, which included American and European children, it was found that probiotic supplementation was associated with a decreased probability of islet autoimmunity, but only in those with the high-risk genotype (DR3/4). The absence of any benefit in other genotypes may indicate a therapeutic strategy for high-risk individuals [85]. However, more research will be needed before implementing this kind of treatment, including genetics, the effect of infections, and the influence of the many other factors that affect microbiota profiles.

COVID-19 Infection

Probable mechanisms for the adverse outcomes in patients with uncontrolled type 1 diabetes secondary to COVID-19 include alteration of the innate and adaptive immune response (due to elevation in TH1, Th2, and Th17 and reduced Tregs), chronic inflammation (insulin resistance and elevated cytokines), endothelial dysfunction (activation of pro-inflammatory cytokines and the cascade of coagulation due to the release of pro-coagulant molecules), oxidative stress (overproduction of superoxide), and the deregulation of the expression of angiotensin II converter enzyme on β cells [86]. In addition to its participation in viral transmission, it has been suggested that the angiotensin II converter enzyme receptor may also contribute to the outcome of new-onset type 1 diabetes with secondary ketoacidosis [87]. It has been noted that COVID-19 reduces ACE2, leading to hypokalemia, as well as lung damage. The reduction in ACE2 also leads to increased angiotensin II levels, which in turn may alter glucose metabolism [88]. However, as noted by

Francisco Rubin, while type 1 diabetes poses a risk of developing COVID-19, the latter is also a trigger for new-onset T1D [89].

The Role of NKT Cells in the Physiopathology of Type 1 Diabetes

Finally, the participation of the autoimmune response in type 1 diabetes is due to an alteration in the regulatory mechanisms of acquired autoimmunity, which corresponds to the expansion and/or function of populations of regulatory T lymphocytes.

The interaction of the innate and adaptive immune systems is definitive in the genesis of the disease. Immune system responses are complex and have evolved to protect multicellular organisms from aggressors; evolutionary pressure has specialized the effecting functions that may also damage the organism's tissue. The immune system specialized in two arms: the innate, capable of mounting nonspecific responses quickly, and the adaptive, capable of promoting longer-lasting, specific responses. Evolution has given rise to specialized cells to carry out these functions. There are some cells that have mixed abilities, that is, both innate and adaptive. This cellular group may be key to understanding the physiopathology of various autoimmune diseases, including T1D. They have recently been linked to type 2 diabetes as well [90]. They share functions and cellular surface markers in both arms. In addition, their evolutionary permanence among species makes them an important link in the homeostatic regulation of the immune system.

To date, the regulatory cell population has not been accurately identified, but there are various candidates, including T lymphocytes CD4+CD25+ and natural killer lymphocyte-type (NKT) cells. NKT cells were identified in 1987 in mice [91], and later their counterpart was described in humans [92]. They are a population of lymphocytes that express the receptor for T lymphocyte antigen (TCR), as well as the common marker of NK cells (NK 1.1 for mice and CD161 in humans). Said heterogeneous population can be $CD4^{+}$, or $CD4^{-}CD8^{-}$ (double negatives), or even $CD8^{+}$; these express a repertoire of conserved TCR [93], in humans made up of variable regions Vα24 and Vβ11. Unlike most T cells, NKT cells recognize lipids in the presence of CD1d molecules. They respond to antigens presented in the context of CD1d molecules, and their important regulatory function is mediated by the secretion of cytokines: INF-δ or IL-4 [94]. NKT cells are found in significant numbers at the site of inflammation and may be a marker of diabetes risk. The frequency of NKT cells is associated with the relative frequency of specific tolerogenic dendritic cell subsets. It appears that NKT cells regulate diabetes, then, by influencing the frequency and possibly the function of dendritic cell subsets, as suggested by Naumov et al. in their work with nonobese diabetic (NOD) mouse models [95]. In addition to playing a key role against bacteria, viruses, and parasites, they are involved in the body's defense against tumors, as well as immune regulation.

In terms of autoimmunity and inflammation, the main results come from the prevention of diabetes in NOD mice [96]. Various studies show a defect in the number and function of NKT cells in these mice, so the disease may be reduced through the adoptive transfer of populations rich in NKT cells [97–100].

The numerical and functional deficiency of NKT cells (detected in the thymus and spleen of NOD mice at 3 weeks of age) mediates the pathogenesis of type 1 diabetes, but the phase of development of T cells in which this deficiency occurs is still unknown. Wagner et al. propose that conventional T cells and doubly negative NKT have a common lineage and that this lineage in the development of the thymus of NOD mice is defective [101]. Some evidence suggests that a deficiency in NKT cells may be coded by risk genes IDD9 and IDD6 (locus Idd9.1, Idd6, Nkt1, and NKt2) for the disease [102–104].

In the last 10 years, studies in humans have documented a decrease in the number and production capability of IL-4 [105] of NKT cells in patients with T1D, while others have described an increase in the frequency of these cells [106–108].

On the other hand, both the frequency of NKT and the production of IL-4 are maintained during the course of type 1 diabetes. Recently, in Colombian patients, upon comparing a healthy control group with type 1 and type 2 diabetes and autoimmune thyroid alterations, no differences were found between the group with type 1 diabetes and healthy controls, but the levels of NKT cells were found to be elevated in type 2 diabetes [109].

The discrepancy in the data seems to come from the type of population selected for the study, as well as the status of the patient in relation to the natural history of the disease, or the subpopulation of NKT cells quantified in those studies since it has recently been suggested that the subset of CD4+ NKT cells may be activated in the prevention of autoimmunity while the subset of double negative NKT (CD4− CD8−) may be pathogenic; to prove this hypothesis, a new monoclonal antibody (6B11) was used to identify the subpopulations of NKT and thus evaluate the individuals at risk and with type 1 diabetes. The results showed an increase and expansion of double negative NKT cells ($CD4^{-}CD8^{-}$) in patients at risk [110].

In Mexico, the incidence of T1D has been on the rise [111]. It is imperative to search for mechanisms that explain the pathophysiology of this disease. To this end, our work group began working with children with type 1 diabetes and their first-degree relatives, where we found a reduction in

NKT cells, in addition to identifying in these cells two populations, a majority one that expressed an elevated quantity of invariant TCR (Vα24/Vβ11) and another minority population that expressed a low density of invariant TCR [112–114]. In this subpopulation, we found that they expressed the activation marker CRTAM (class I restricted T cell-associated molecule) [112]. CRTAM is also expressed on $CD4^+$ and $CD8^+$ T cells and is associated with the inflammatory process. Both CRTAM and CD69 are expressed in NKT cells with low invariant TCR, suggesting a state of activation [113]. In addition, a clear association has been observed between the expression of CRTAM and the production of IFN-γ in NKT cells in both healthy individuals and those with type 1 diabetes, which suggests that CRTAM can be used as a marker to identify the NKT cells [115].

On the other hand, in Class II MHC molecules, cathepsin-L lysosomal protease (CTSL) exercises broad influence on the immune system and has an important role in the expression of antigen-presenting cells. In CTSL nkt/nkt mice, it has been shown that the activity of the CTSL gene impacts the positive selection of CD4+ thymocytes and regulates the level of expression of various components of the extracellular matrix in lymphoid organs, influencing the number and composition of central and peripheral T lymphoids [116]. However, to date, the role of NKT cells and CTSL gene expression has not been clearly established in humans as a biomarker in the physiopathology of type 1 diabetes. In the belief that CTSL is involved in the promotion of the survival of cytotoxic T lymphocytes, it was recently shown that the percentage and absolute numbers of NKT cells correlate with low levels of expression of the CTSL gene in T1D in humans [117].

To date, the complete pathogenesis of type 1 diabetes remains unknown. It is known that the process of developing this disease involves a myriad of factors.

Genetically, 50% of susceptibility to T1D can be associated with HLA genes, and the other 50% with non-HLA genes, such as PTPN22, CTLA-4, and IFIH1. Research continues to identify new candidates for the latter. The alleles that indicate risk or protection from the development of T1D vary with country and ethnicity. In addition, the presence of two or more autoantigen antibodies is an important indicator of risk.

It is possible that the drastic increase in the prevalence of T1D is largely due to the implicated environmental factors. Technological advances have helped identify genetic overexpression in reaction insulitis. Dysbiosis is involved in alterations in the immune system and has been linked to the pathogenesis of T1D. Current studies are focusing on this important aspect of the epigenetics of the disease.

Finally, NKT cells are found in significant numbers at the site of inflammation and may be a marker of diabetes risk. Their participation in both innate and adaptive autoimmunity has made them a target of interest. The clinical value of this tool remains under investigation.

Multiple-Choice Questions

1. Type 1 diabetes
   (a) Is diagnosed only in children
   (b) Has a silent period before manifestation and diagnosis
   (c) Is diagnosed during pregnancy
   (d) Is often confused with type 2 diabetes
   (b) It has a silent period before manifestation and diagnosis
2. Which of the following is **not** a factor in the development of T1D?
   (a) Microbiota
   (b) Environmental factors
   (c) Immunological factors
   (d) Alterations in insulin secretion
   (d) Alterations in insulin secretion are a factor for type 2 diabetes
3. The genotype that combines the two susceptibility haplotypes (DR4-DQ8/DR3-DQ2)
   (a) increases the risk of T1D
   (b) has no effect on the disease
   (c) never appears in relatives
   (d) always appears in relatives
   (a) The genotype that combines the two susceptibility haplotypes (DR4-DQ8/DR3-DQ2) increases the risk of contracting the disease.
4. HLA genes
   (a) Are responsible for all of T1D genetic susceptibility
   (b) Are not responsible for T1D genetic susceptibility
   (c) Are partially responsible for T1D genetic susceptibility
   (d) Have no connection with T1D susceptibility
   (c) T1D is a multifactorial disease, where HLA genes have around 50% of the genetic responsibility for T1D susceptibility. The other 50% comes from non-HLA genes.
5. Which of the following non-HLA genes is associated with T1D?
   (a) PTPN22
   (b) TCF7L2
   (c) SCL16A11
   (d) DRB1-DQB1
   (a) PTPN22 associates with T1D.
6. Insulitis has been associated with
   (a) Age at disease onset
   (b) Elderly patients
   (c) Time with diabetes
   (d) Patient siblings

(c) Insulitis has an inverse correlation with time with diabetes.

7. All of the following have been associated with T1D except
   (a) rubella
   (b) Coxsackie B
   (c) enterovirus
   (d) parvovirus

   (d) Parvovirus has not been shown to have an association with human T1D.
8. In children with type 1 diabetes, NKT cell populations usually
   (a) Are increased
   (b) Are not present
   (c) Are reduced
   (d) Are hyperactive

   (c) NKT cells are usually reduced in frequency in children with T1D.
9. Which mechanisms are not associated with adverse outcomes of COVID-19 in patients with type 1 diabetes?
   (a) Elevation of TH1, TH2, and TH17
   (b) Chronic inflammation
   (c) Oxidative stress
   (d) Age at onset of T1D

   (d) To date, no clear association has been observed between the age at the onset of type 1 diabetes in children or adults.
10. The quantification of antibodies against autoantigens in T1D helps us know all of the following **except**
    (a) The activity of the disease
    (b) Time since the onset of the disease
    (c) The degree of progression of the disease
    (d) Prediction of the clinical status of disease

    (b) The quantification of antibodies against autoantigens has been useful in knowing the activity of the disease, determining its degree of progression, and contributing to the classification and prediction of the clinical status of the patients.

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Pathophysiology of Type 2 Diabetes

9

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Glucose Homeostasis

In healthy individuals, normal glucose homeostasis in the basal or post-absorptive state is maintained, despite wide fluctuations in supply and demand, by means of a highly regulated and dynamic interaction between tissue sensitivity to insulin and insulin secretion. While maintenance of plasma and tissue glucose levels is required for vital functions of the brain, elevated glucose levels are deleterious or toxic to the vascular endothelium and a myriad of other vital tissues. Normally, in the postabsorptive state, most of the glucose utilization occurs in insulin-independent tissues like brain (50%) and splanchnic areas (25%) while the rest occurs in insulin-dependent tissues like muscles and adipose tissue. The insulin secretion during the next 2 h depends on the glucose disposal rate and the degree of suppression of hepatic glucose production (HGP). Additionally, insulin stimulates lipoprotein lipase in the vascular endothelium and promotes lipolysis and the removal of chylomicrons and VLDL from circulation. A derangement in the appropriate β-cell insulin secretion or insulin action at the level of muscle, liver, and adipose tissue foregoes the hyperglycemic states of prediabetic and diabetic states [1, 2].

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Pathophysiology of Type 2 Diabetes

Individuals at risk of T2D are thought to inherit a genetic predisposition to insulin resistance [3, 4]. Chronic fuel excess is the chief pathogenic event that triggers T2D development in these genetically and/or epigenetically susceptible individuals [5]. In states of normal insulin sensitivity, HGP is suppressed by insulin. However, in the event of hepatic IR, gluconeogenesis continues during the basal state even when the fasting insulin level is high and leads to hyperglycemia [6]. During the fed state, suppression of HGP in response to insulin is impaired as well [7]. With peripheral tissue IR, post-meal glucose uptake ensues, and postprandial hyperglycemia sets in [7]. The current epidemic of obesity and physical inactivity [8] are IR states [9] that unmask the pancreatic β-cell defect when they fail to augment insulin secretion to offset the effects of IR [3, 10]. As long as the β-cells are able to enhance their insulin secretion to compensate for the impact of IR, glucose tolerance/euglycemia is maintained [11]. However, with time, β-cells become unable to compensate for the IR, and initially, the postprandial plasma glucose (PPG) levels and later the fasting plasma glucose (FPG) levels begin to rise, leading to overt diabetes. Individuals in the upper tertile of impaired glucose tolerance (IGT) are highly insulin-resistant and would have lost 80% of their β-cell function [10, 12].

In 1987, DeFronzo put forward the concept that T2D resulted from deficits in the pancreatic β-cell, muscle, and the liver, which were collectively referred to as the "Triumvirate" (see Fig. 9.1) [12, 13].

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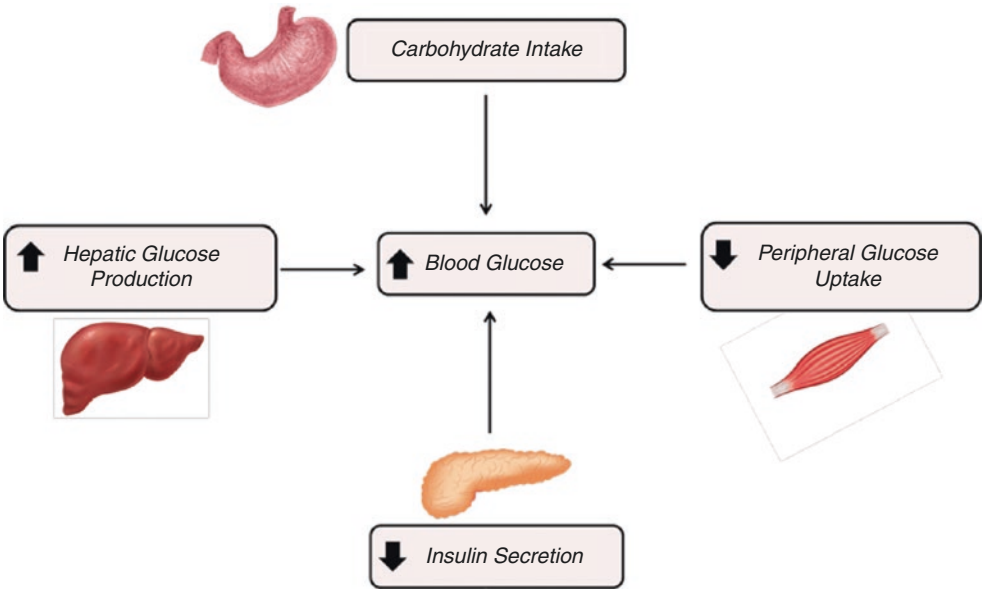

Fig. 9.1 The Triumvirate: The core physiological defects that were earlier proposed to be involved in type 2 diabetes pathogenesis [10]. (*Adapted from Chawla R. Manual of Diabetes Care: Jaypee Brothers, Medical Publishers Pvt. Limited; 2014*)

In addition to the triumvirate, numerous other factors have been demonstrated to contribute to T2D pathophysiology. In his Banting Lecture, Defronzo revealed some of the other players, viz., adipocytes (accelerated lipolysis), incretin defect, α-cells (hyperglucagonemia), kidney (increased glucose reabsorption), and brain (neurotransmitter dysfunction and central appetite dysregulation), that play important roles in the development of glucose intolerance in T2D individuals [10]. Collectively, these eight players were named the "ominous octet" [12].

The cast list in T2D pathophysiology is still being unraveled. In 2013, Kalra et al. suggested that another four factors responsible for T2D be added to the list of ominous octets, viz., dopamine, vitamin D, testosterone, and the renin-angiotensin system (RAS), and labeled all 12 factors as the "dirty dozen" [14]. In 2016, Somasundaram and Wijesinghe proposed a 13th mechanism—the role of gut and gut microbiota in T2D [15]. Other factors such as iron overload and gut-derived serotonin have also been proposed to have a role in T2D development [16].

The Ominous Octet

β-Cell Dysfunction

β-cell dysfunction plays a major role in T2D development, across the spectrum of hyperglycemia, from prediabetes to overt diabetes. These cells are in a constant state of dynamic change, with continued regeneration of islets and simultaneous apoptosis. This delicate balance can be disrupted by multiple abnormalities. As the β-cell failure progresses, insulin secretion becomes inadequate to avert the rising blood glucose levels [1]. Although the plasma insulin response to IR is usually increased during the natural history of T2D, this does not imply that the β-cell is functioning normally. In fact, the onset of β-cell failure is found to occur much earlier, and the contribution to hyperglycemia is, in fact, more severe than previously appreciated [10]. For as long as the β-cells are able to augment insulin secretion sufficiently to overcome IR, glucose tolerance remains within limits. β-cell responds to an increment in glucose (ΔG) with an increment in insulin (ΔI) and $\Delta I/\Delta G$ was initially considered the measure of β-cell function. The β-cell also takes into account the severity of IR and accordingly adjusts insulin secretion. Thus the gold standard to measure β-cell function is the insulin secretion/IR, i.e., $\Delta I/\Delta G \div$ IR, known as the glucose disposition, index [17]. In individuals susceptible to T2D, there is a limitation to this hypersecretion of insulin. The insulin secretion/IR index seen in normal glucose-tolerant (NGT), IGT, and T2D individuals as a function of the 2 h PPG during an oral glucose tolerance test (OGTT) is shown in Fig. 9.2. The onset of T2D is not associated with a further deterioration in insulin sensitivity, but rather insulin secretion that wanes and fails to compensate for the prevailing IR [18]. Individuals in the upper tertile of "normal" glucose tolerance (2-h PG = 120–139 mg/dL, i.e., 6.7–7.7 mmol/L) would have lost two-thirds of their β-cell function (see first arrow in Fig. 9.2), while subjects in the upper tertile of IGT (2-h PG = 180–199 mg/dL, i.e., 10.0–11.1 mmol/L) would have lost 80–85% of their β-cell function (see second arrow in Fig. 9.2) [10, 19–21]. Concisely, although IR in liver/muscle is well established early in the natural history of T2D, overt diabetes will not develop in the absence of progressive β-cell failure [12]. Also, with the acquisition of recent knowledge, it appears that β-cells may become dedifferentiated in people with T2DM and that these dedifferentiated cells may convert to other cell types such as glucagon-secreting α-cells [22].

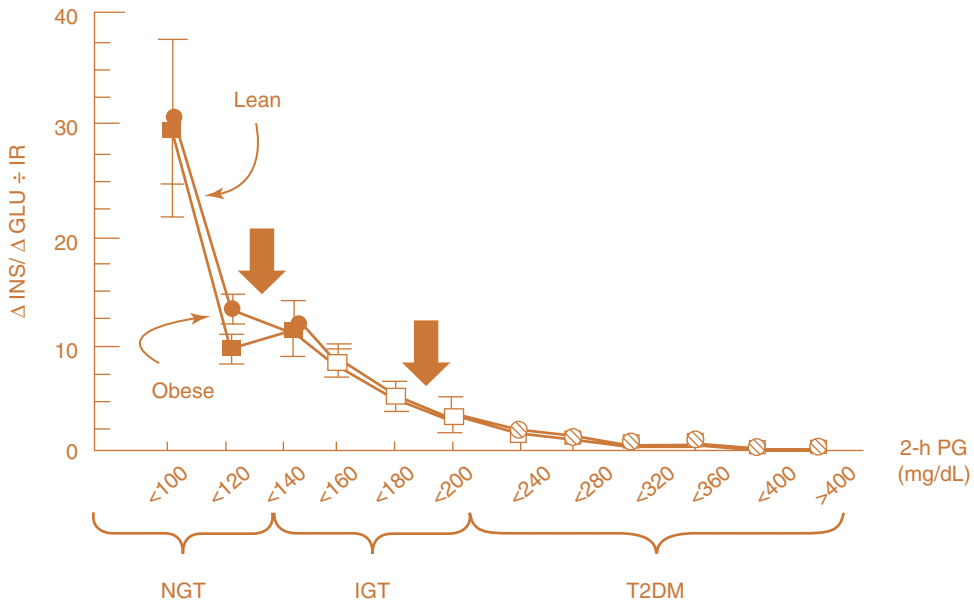

Fig. 9.2 Insulin secretion/insulin resistance (disposition) index in subjects with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and type 2 diabetes (T2D) as a function of 2 h PPG in lean (closed circle) and obese (open circle) individuals [10]. *(Adapted from DeFronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58(4):773-95)*

Age and genes are two well-known non-modifiable factors which influence the state of β-cell health. A progressive age-related decline occurs in β-cell function [23], and the incidence of diabetes is found to increase with advancing age. β-cell failure clusters in families, and a number of genes have been associated with T2D in people from multiple ethnic backgrounds. Most common are the transcription factors associated with β-cell dysfunction (e.g., the T-allele of single nucleotide polymorphism rs7903146 of the TCF7L2 gene) [4, 24, 25]. However, the modifiable contributors to insulin secretion and IR, e.g., lipotoxicity, glucotoxicity, and incretin defects, can improve β-cell function and should be sought [10, 26]. Hypersecretion of islet amyloid polypeptide (co-secreted with insulin) gives way to subsequent amyloid deposition within the pancreas, and it is speculated to be involved with disease progression rather than initiation [27, 28] (see Fig. 9.3).

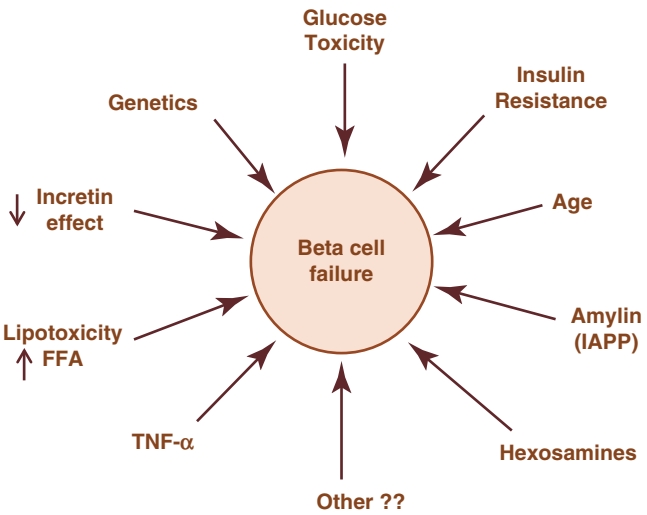

Fig. 9.3 Pathogenic factors implicated in progressive β-cell failure [26]. *(Adapted from DeFronzo RA, Ferrannini E, Alberti KGMM, Zimmet P, Alberti G. International Textbook of Diabetes Mellitus, 2 Volume Set: Wiley; 2015)*

Insulin Resistance

Insulin resistance is the diminished ability of insulin to exert its biological action across a broad range of concentrations [29]. Relatively high insulin levels observed during fasting and in response to insulin secretagogues are indicative of IR. Insulin resistance is a consistent finding in T2D, and it may appear many years before the disease's onset. It is also a well-known associate of obesity, and many obese individuals develop T2D. Interestingly, some patients, despite being obese, never develop T2D, highlighting the significant contribution of the β-cell deficit in individuals who develop T2D. Important to note, physical activity has a significant positive effect on insulin sensitivity, even when correcting for confounding factors such as being overweight. What's more, during the latter half of pregnancy, even in women with normal glucose homeostasis, IR increases due to the production of placentally derived hormones like human placental lactogen. Gestational diabetes mellitus (GDM) ensues if the maternal β-cells are unable to produce sufficient insulin to overcome the IR. Insulin resistance is mediated at three organ levels—liver, muscle, and adipose tissue. Much more than the mere IR, the triad of factors contributes to the biochemical potpourri of diabetes [1, 16].

Hepatic Insulin Resistance

Insulin resistance in the liver is manifested by glucose overproduction during the basal state despite fasting hyperinsu-

linemia [6] and impaired suppression of HGP by insulin [30], following a meal [7]. Due to its obligate need for glucose, the brain uses up more than half of the glucose produced. This glucose demand is met primarily by the liver and, to a lesser extent, by the kidneys [31]. Normally, the liver produces 2 mg/kg per min of glucose, whereas in diabetes-affected individuals, this basal rate of HGP is increased to 2.5 mg/kg per min. This increased HGP occurs even when the fasting plasma insulin levels are increased 2.5- to 3-fold, indicating severe resistance to the suppressive effect of insulin on HGP.

In the early stages of T2D, postprandial hyperglycemia is attributed to, reduced glucose uptake by the muscles, and during the postabsorptive period, the fasting levels are maintained by HGP. Both sources of HGP, glycogenolysis, and gluconeogenesis, are under insulin control. But in the IR state, the latter accounts for nearly the entire increase in hepatic glucose output. Around one-fourth of the glucose derived from a meal is extracted by the liver during the recycling of portal and systemic blood, and insulin is suggested to facilitate the storage of this glucose as glycogen. Gluconeogenesis accounts for even greater amounts of glycogen. Moreover, during active gluconeogenesis, glycogenolysis is inhibited and results in excess hepatic glycogen [32] in uncontrolled diabetes. The accelerated gluconeogenesis in T2D can be due to elevated circulating levels of precursor molecules like lactate and alanine from the muscles and glycerol from the adipose tissue. A simultaneous upsurge in free fatty acids (FFA) and concomitant hyperglucagonemia facilitate gluconeogenesis. Insulin resistance also stimulates VLDL and apo-B synthesis in the liver, while HDL is lowered due to a greater exchange of cholesterol ester transport proteins. An increase in small dense low-density lipoprotein particles is also noted during the process [13].

Muscle Insulin Resistance

In the muscle, IR is manifested by impaired glucose uptake after carbohydrate ingestion, resulting in postprandial hyperglycemia [30, 33, 34]. In the insulin-stimulated post-prandial state, skeletal muscle accounts for more than 75% of the excess glucose uptake [35], and in diabetes patients, it accounts for the largest part of the impairment of glucose disposal. Adipose tissue mass being smaller in size accounts for the rest, whereas there may not be any change in the case of brain and splanchnic tissues [1]. In T2D, the muscle IR accounts for more than 85–90% of the impairment in total body glucose disposal [3, 13, 33, 34].

Adipose Tissue Insulin Resistance

Though deranged adipocyte metabolism was initially not considered to play a significant role in T2D pathogenesis, later on, evidences supported the adipose tissue being considered the "fourth musketeer" along with the triumvirate [10, 36, 37]. In healthy individuals, insulin exerts an anti-lipolytic effect on fat cells, whereas in T2D individuals, IR prevents insulin from exerting its anti-lipolytic effect. The result is sustained lipolysis with a day-long elevation in plasma free fatty acid (FFA) levels. This, in turn, stimulates gluconeogenesis, induces hepatic and muscle IR, and impairs β-cell function (lipotoxicity). FFAs also enhance the activity of glucose-6-phosphatase, which ultimately controls the release of glucose by the liver [38]. Dysfunctional adipocytes produce pro-inflammatory adipocytokines in excess (IL-6, TNF-α, leptin, visfatin, etc.), which induce IR and atherosclerosis. This also induces a feed-forward process in which activation of transcription factors leads to further pro-inflammatory cytokine production [39, 40]. Deranged adipocytes also tend to secrete subnormal amounts of insulin-sensitizing adipocytokines (e.g., adiponectin). Enlarged fat cells are insulin-resistant and have a lesser capacity to store fat. When the storage capacity of adipocytes is exceeded, lipid "overflows" into muscle, liver, β-cells, and arterial vascular smooth muscle cells, leading to muscle and hepatic IR, impaired insulin secretion, and acceleration of atherosclerosis [41].

Meanwhile, the discovery of functional brown adipose tissue raised the possibility of its involvement in human energy homeostasis and in preventing T2D. The detectability of this tissue lessens with age, high BMI, and high FPG [5, 42]. A healthy obese state has been entertained, and the theory is based on the existence of differences in IR between adipose deposition sites. In other words, adipose site-specific IR with intra-abdominal adipose tissue is seemingly more insulin-resistant and harmful than subcutaneous adipose tissue (SAP). The former has particularities related to higher lipolysis, higher release of adipokines, etc., which are longitudinally associated with an increased risk of incident metabolic syndrome (MetS) [43]. In individuals who remain resistant to T2D, excess calories are safely partitioned to SAP rather than to the muscle, liver, heart, and β-cells, thus avoiding damage to the key organs. Major mechanisms for such protective effects include β-cell compensation, maintenance of near-normal blood nutrient levels, development of minimal IR, increased expansion of SAT relative to visceral adipose tissue, and limited increase in liver fat [5].

Alpha Cells (Increased Glucagon Secretion)

In as early as the 1970s, it was established that T2D individuals have elevated plasma glucagon levels [44–46]. While a reduction in β-cell mass is seen in diabetes patients as compared to normal individuals, there occurs no reduction in the α-cell mass. It is also proposed that β-cells dedifferentiate in T2D individuals and get converted to other cell types like glucagon-secreting α-cells [22]. Substantiating these, even when insulin levels progressively decline over

the course of T2D, basal glucagon levels tend to remain elevated [47, 48]. The role of hyperglucagonemia in the maintenance of increased rates of HGP in T2D was demonstrated by Baron et al. [49]. In T2D, fasting glucagon levels are elevated and the postprandial glucagon levels are not suppressed, but paradoxically elevated. These raised blood glucagon levels increase the HGP, leading to an elevation in FPG and PPG levels, resulting in a worsening of diabetes [48, 50].

Upon somatostatin infusion, there were declines in plasma glucagon levels by 44% and in basal HGP by 58%. When somatostatin was administered to alloxan-diabetic dogs [51] or to insulin-deprived T2D subjects [52], hyperglucagonemia was suppressed and hyperglycemia was reduced, even though insulin had been reduced or discontinued. Many other studies also support the prime role played by glucagon in T2D pathogenesis [44, 53, 54]. The drugs capable of inhibiting glucagon secretion or blocking the glucagon receptor have now proven effective in treating T2D [55–57].

Incretin Defect

Glucose ingestion can elicit a higher insulin response than an intravenous infusion, which is explained by the incretin effect. The incretin hormones, glucagon-like peptide-1 (GLP-1) secreted by the L-cells of the distal small intestine and glucose-dependent insulinotropic peptide (GIP) by the K-cells of the more proximal small intestine, collectively act on the pancreatic islet [10, 39, 58, 59]. Of these, GLP-1 acts on the β-cells to increase insulin and on the α-cells to suppress glucagon secretion [58]. GLP-1 thus imparts an indirect benefit on β-cell workload, since a reduction in glucagon levels leads to a reduced postprandial HGP. Gut hormones, including GLP-1, also have roles in the central nervous system's (CNS) regulation of energy balance and appetite [5, 60]. GLP-1 delays the rate of gastric emptying, results in a feeling of fullness and satiety, and is therefore associated with the control of weight gain [10, 61, 62]. In T2D, the incretin effect is substantially impaired possibly due to impaired GLP-1 production and reduced sensitivity of β-cells to GIP [5, 63, 64]. Dysfunction in glucagon secretion due to impaired incretin action is also suggested [65]. In subjects with NGT, IGT, or T2D, plasma GLP-1 levels do not seem to differ much [65], which suggests that the β-cell response to GLP-1 following meal ingestion is deficient, as seen during intravenous administration of GLP-1 under controlled conditions [66]. Elevations in GLP-1 levels are reported after bariatric surgery, which might partially explain the multiple beneficial effects of this intervention, especially among T2D individuals [39]. Numerous pharmacologic approaches are available nowadays that effectively harness the potential of incretins to treat diabetes, which include GLP-1 agonists and DPP4 inhibitors [67].

Kidneys (Increased Glucose Reabsorption)

The kidney's adaptive response to conserve glucose, which enables it to meet the energy demands of the body, especially the brain and other neural issues, which have an obligate need for glucose, becomes maladaptive in diabetes. Rather than draining out the glucose into urine to correct the hyperglycemia, the kidney retains the glucose. Normally, the kidney filters around 162 g of glucose daily, and the high-capacity SGLT2 transporter in the convoluted segment of the proximal tubule reabsorbs almost 90% of the filtered glucose, while the remaining 10% is reabsorbed by the SGLT1 transporter in the straight segment of the descending proximal tubule [68]. In both T1D and T2D, the maximum renal tubular reabsorptive capacity (Tm) for glucose is higher [69–72]. Therefore, in normal individuals, no glucose appears in the urine until the plasma glucose level is >180 mg/dL [73], whereas in T2D, this threshold is much higher [71]. Medications to inhibit renal proximal tubular glucose reabsorption were thus thought out to treat T2D [68]. SGLT2 inhibitors confer multiple benefits like better glycemic control by improving β-cell function and insulin sensitivity, reductions in body weight and blood pressure, etc. [74]. Currently, therapies aimed at inhibiting the SGLT1 receptors in the gut and downstream from the SGLT2 receptors in the kidney are also underway [75–77].

Brain (Neurotransmitter Dysfunction and Central Appetite Dysregulation)

The nervous system also plays a key role in T2D pathogenesis. Sympathetic and parasympathetic nervous systems control glucose metabolism directly through neuronal input and indirectly via circulation to regulate insulin and glucagon release and HGP [39, 78]. Severing the vagus nerve impaired insulin secretion, revealing its important role in regulating the islet [79]. Ablation of the hypothalamus leads to β-cell dysregulation and subsequent hyperinsulinemia [80]. Insulin has a powerful appetite-suppressing effect [81]. However, in obese individuals with or without diabetes, even though IR results in compensatory hyperinsulinemia, food intake seems to be higher, indicating that the appetite centers are also IR. In a functional magnetic resonance imaging study where the cerebral response to ingested glucose was examined [82], consistent inhibition was noted in the lower posterior (which contains the ventromedial nuclei) and upper posterior (which contains the paraventricular nuclei) hypothalamus upon glucose ingestion. Both of these areas are key appetite regulation centers, and the extent of inhibitory response upon glucose ingestion was decreased in these areas in obese, insulin-resistant subjects even when euglycemic. A delay was also observed in the time taken to reach the maximum inhibitory response in these individuals even in the presence of a high plasma insulin response. Further studies have also indicated that cerebral IR leads to increased HGP and

reduced muscle glucose uptake [83, 84]. High-fat diet-fed rodents are prone to inflammation-induced neuronal injury, and in humans, structural changes in the hypothalamus have been observed in keeping with gliosis in obese compared to lean individuals [85]. Reduced dopamine levels in the hypothalamus and increased catecholamine levels in the CNS also contribute to appetite dysregulation and are suggested to directly cause IR in liver and peripheral tissues [84, 86]. The neuroendocrine hormone amylin is also deficient in T1D and T2D [15], and its effect on appetite dysregulation is suggested to be chiefly mediated via central pathways that include high-affinity binding sites in the area postrema in the hindbrain [87]. It also has direct gut effects through a decrease in the rate of gastric emptying [88]. Clock genes located in the brain which are major determinants of circadian rhythmicity, together with sleep, are now being investigated due to their role in metabolic processes [89, 90].

The "Dirty Dozen," the "Unlucky Thirteen," and Much More

Dopamine

Dopamine, the most abundant catecholamine in the brain, has been nicknamed the "forgotten felon" of diabetes [16], and along with the other catecholamines of the autonomic nervous system, this neurotransmitter modulates glycemia. It was Kalra et al. who proposed the specific addition of the dopaminergic system as a ninth contributor to T2D development [91]. Mammalian species have an inherent capacity to alter their metabolism from the insulin-sensitive/glucose-tolerant state to the insulin-resistant/glucose-intolerant state at exactly the right time of the year to meet the varying energy demands. Such seasonal metabolic changes are governed by the changes in monoaminergic concentrations/activity in the suprachiasmatic nuclei (SCN) of the hypothalamus—the mammalian circadian pacemaker—and in the ventromedial hypothalamus (VMH). Development of an IR state during such seasonal changes exactly mimics the T2D state: muscle and hepatic IR, increased HGP/gluconeogenesis, hyperglycemia, adipocyte IR and enhanced lipolysis, increased plasma FFA and triglyceride levels, and obesity. Evidences implicate endogenous dopaminergic and serotonergic rhythms in SCN and VMH in the transition from the insulin-sensitive to insulin-resistant state. In animals that undergo seasonal changes in metabolism, within the VMH, during the insulin-resistant state, both serotonin and noradrenergic levels and activity are enhanced and decrease to normal levels upon returning to the insulin-sensitive state. On the contrary, dopamine levels decrease during the IR state and increase to normal following the return of the insulin-sensitive state. A selective destruction of dopaminergic neurons in the SCN of the hypothalamus resulted in severe IR [86, 92, 93].

Both systemic [94, 95] and intracerebral [96] bromocriptine (a sympatholytic D2-dopamine agonist) administration to insulin-resistant animals decreased the elevated VMH noradrenergic and serotonergic levels with a resultant decline in HGP, reduced adipose tissue lipolysis, and improved insulin sensitivity. In T2D and obese nondiabetic individuals, systemic bromocriptine administration improved glycemic control and dyslipidemia without changes in body weight [97]. It was postulated that in T2D patients, hypothalamic dopamine reduces in the early morning, leading to elevated HGP and lipolysis, resulting in glucose intolerance, IR, and dyslipidemia. Timed bromocriptine (quick-release formulation) administration within 2 h of awakening augmented low hypothalamic dopamine levels and decreased the sympathetic tone within the CNS, leading to an increase in insulin sensitivity, suppression of HGP, and thereby a reduction in PPG levels [86].

Vitamin D

Vitamin D subserves a range of biological functions like cell differentiation, inhibition of cell growth, and immunomodulation. Both direct and indirect effects of vitamin D on various mechanisms related to the T1D and T2D pathophysiologies have been postulated, including pancreatic β-cell dysfunction, impaired insulin action, systemic inflammation, and apoptosis. Over the past decade, vitamin D has emerged as a potential risk determinant for type 2 diabetes. Vitamin D receptors occur in all tissues and organs that are involved in these diseases, and the machinery for producing vitamin D locally is also present in islets, immune cells, and other tissues involved [14, 98–100]. Owing to the broad tissue distribution of the vitamin D receptor (VDR) and extrarenal activation of 25(OH)D to $1,25(OH)_2D$, vitamin D imparts extraskeletal effects. Consequently, a low level of 25(OH)D has been found to be associated with the risk of developing type 2 diabetes [101]. Various factors such as body weight and fatness, assessed by the body mass index (BMI), influence the blood 25(OH)D level. Specifically, a higher BMI is associated with a lower blood 25(OH)D level and hence with an increased risk of diabetes [102]. Children receiving the recommended dose of vitamin D during the first year of life had an 80% reduced T1D risk [103]. Lower vitamin D levels might result in impaired β-cell function with lowered insulin secretion and sensitivity and higher IR [104], and might also pose a risk for developing macrovascular and microvascular complications [105]. Among Caucasian children and adolescents, low vitamin D levels were associated with total adiposity, MetS, and hypertension [106]. Vitamin D supplementation in T2D and nondiabetic subjects imparts beneficial effects on glucose homeostasis and other markers

of MetS like improving β-cell function and insulin secretion and reducing IR [107, 108]. Solutions to clinically relevant queries are rarely dichotomous ("positive" or "negative"), and a recommendation of whether "to D or not to D" should be made based on the available data from both observational studies and clinical trials. However, results from the trials are congruent with mounting evidence from observational studies highlighting the role of vitamin D in regulating diabetes risk.

Renin-Angiotensin System

Evidences suggest a role for the RAS in the development of IR and T2D [109, 110]. Detrimental effects that RAS has on insulin secretion are mediated by a decrease in pancreatic blood flow and induction of islet fibrosis, oxidative stress, and inflammation, whereas both impaired skeletal muscle function (disturbances in skeletal muscle blood flow, insulin signaling, and mitochondrial function) and adipose tissue (AT) dysfunction (adipocyte hypertrophy, inflammation, and impairments in AT blood flow and lipid metabolism) may contribute to RAS-induced IR [110]. Frequent association of T2D with hypertension, retinopathy, nephropathy, and cardiovascular disease (CVD) has also implicated RAS in the initiation and progression of these disorders.

RAS blockade significantly improves insulin sensitivity [111–113] and significantly reduces the incidence of vascular complications in T2D [114–116]. Such improvements are postulated to be due to the improvement of blood flow and microcirculation in skeletal muscles, decrease in adipocyte size, protective actions on pancreatic islets, etc., thereby facilitating insulin signaling at the cellular level and improvement of insulin secretion by pancreatic β-cells [15, 117–120]. Among high-risk populations, RAS blockade using either angiotensin II receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACEI) led to a 22% reduction in the incidence of new-onset T2D [121]. The DREAM study in individuals without CVD but with impaired fasting glucose levels or IGT showed that the ACEI ramipril did not significantly reduce the diabetes incidence or death but significantly increased the regression to normoglycemia [122]. The NAVIGATOR study among individuals with IGT and CVD or risk factors showed that ARB valsartan use, along with lifestyle modification, caused a relative 14% reduction in diabetes incidence but did not reduce the rate of CVD events [123]. Despite the lack of consistency in the findings between many of these trials, subanalyses of some of them have shown that RAS inhibitors improve glucose levels and reduce the risk for diabetes in higher-risk populations [109, 124, 125].

Testosterone

An association between low testosterone and T2DM risk in men is well-proven [126–128]. Morbid obesity imposes negative effects on the hypothalamic-pituitary-gonadal axis in men [129]. A bidirectional relationship between visceral fat and testosterone is suggested, which sets up a self-perpetuating cycle promoting IR and diabetes. High visceral fat increases the secretion of proinflammatory cytokines, estradiol, insulin, and leptin, all of which may inhibit the hypothalamopituitary gonadal axis activity at multiple levels [130, 131]. Decreased testosterone levels also build up IR via mechanisms involving muscle [132], liver [133], and bone [134]. Testosterone decreases IR by regulating mature adipocytes and myocytes. Testosterone also increased catecholamine-induced lipolysis in vitro [135] and decreased lipoprotein lipase activity and triglyceride uptake in abdominal adipose tissue in humans [136]. A positive correlation exists between testosterone levels and insulin sensitivity, and the individuals with hypogonadal testosterone levels had a higher BMI and a higher prevalence of the MetS than their eugonadal counterparts [132]. Other studies including landmark studies like the Massachusetts Male Aging Study (MMAS) and the Multiple Risk Factor Intervention Trial (MRFIT) have all demonstrated an inverse association between low testosterone levels and risk for MetS and diabetes [128, 137–139]. Further, low sex hormone binding globulin (SHBG) may lead to IR and lower total testosterone [140]. Among prostate cancer patients subjected to androgen deprivation therapy (ADT), lower testosterone levels were associated with increased IR [141, 142] and an increased diabetes risk [143]. Testosterone substitution in hypogonadal men improved insulin sensitivity and glycemic control [144, 145]. In men with newly diagnosed diabetes, the addition of testosterone to a regimen of diet and exercise significantly improved the outcomes on glycemic control and reversal of the MetS [145, 146].

Interestingly, the effect of testosterone on IR and T2D is opposite in males and females. Its low concentrations in males but high concentrations in females favor IR and T2D [147–149]. In a systematic review and meta-analysis by Ding et al., endogenous levels of testosterone and SHBG were found to exhibit sex-dependent relations with the risk of T2D. Elevated testosterone levels were linked to greater T2D risk in females but a lower risk in males. Meanwhile, SHBG was more protective in females than in males [149]. Polycystic ovary syndrome (PCOS), characterized by chronic anovulation and hyperandrogenism, was also suggested to have partly contributed to this observed positive testosterone association in females. Insulin resistance with compensatory hyperinsulinemia is the key pathogenic factor in PCOS and can lead to the onset of hyperandrogenism by stimulating ovarian androgen production and by decreasing SHBG levels. Females of reproductive age with PCOS are thus prone to metabolic disorders and T2D [149, 150].

Gut and Gut Microbiota

Gut

Centuries ago, the ancient Greek physician Hippocrates said, "All Disease Begins in the Gut." Mounting evidence strongly supports the above-quoted hypothesis, and in 2016, Somasundaram et al. proposed the role played by the gut as the 13th mechanism in diabetes pathogenesis [15]. Even though the contribution of gastrointestinal (GI) carbohydrate absorption towards T2D pathogenesis had long been known, its contribution was rather underutilized as a target for therapy. Alpha-glucosidase inhibitor (AGI) is the only class of drug that effectively utilizes this mechanism for the treatment of diabetes and has clear beneficial effects on glycemic control and post-load insulin levels [151]. SGLT1 plays a distinct and complementing role to SGLT2 in glucose homeostasis. Within the GI tract, SGLT1 is responsible for glucose absorption and is also involved in 10% of renal glucose reabsorption. Inhibition of SGLT1 and combined inhibition of SGLT1/SGLT2 is thus a new anti-hyperglycemic concept [75–77], which further implies the contribution of GI carbohydrate absorption in T2D pathogenesis.

Bile acids also play a significant role in modulating glucose homeostasis, and bile acid homeostasis is altered in T2D. Bile acids act as signaling molecules through receptor-dependent and receptor-independent pathways [152]. They act as endogenous ligands of the farnesoid X receptor (FXR), and their activation of FXR leads to the release of fibroblast growth factor (FGF) [153]. Through FXR, bile acids suppress the in vitro expression of fructose-1, 6-biphosphatase-1, gluconeogenic phosphoenolpyruvate carboxykinase, and glucose-6-phosphatase [154]. G-protein-coupled receptors TGR5 (also termed GPR131) located on intestinal L-cells are activated by bile acids, resulting in GLP-1 secretion [155]. Intraduodenal bile acid infusion dose-dependently enhanced plasma FGF19 concentrations, with smaller effects on GLP-1 and CCK [156, 157]. FGF19 possesses insulin-like effects, inducing glycogen and protein synthesis while suppressing glucose production [39]. A second-generation bile acid sequestrant colesevelam modestly reduces glucose in T2DM when used as an adjunct to other agents. Suggested mechanisms include its effect on bile acid receptors in the intestine as well as in the liver to reduce endogenous glucose production [15, 158].

Gut Microbiota

Besides the gut, the gut microbiome is also involved in T2D pathogenesis [15, 39, 159, 160]. Gut dysbiosis, intestinal barrier dysfunction, and subsequent metabolic endotoxemia are all closely related to inflammation, IR, and finally CVD events in T2D [161, 162]. Individuals with prediabetes or T2D have a moderate degree of gut microbial dysbiosis in terms of a reduction in the abundance of certain universal butyrate-producing bacteria (*Faecalibacterium prausnitzii*, *Roseburia intestinalis*, etc.) and an increase in various opportunistic pathogens (like *Lactobacillus* sp.) [162, 163]. In individuals with MetS, vancomycin treatment decreased the abundance of butyrate-producing gram-positive bacteria, which correlated well with impaired insulin sensitivity [164]. Decreased levels of butyrate-producing gut microbes in T2D individuals were thus suggested to lead to disease pathogenesis. Among the short-chain fatty acids, butyrate acts as a prominent energy source for intestinal epithelial cells and influences a variety of colonic mucosal functions, reinforcing the colonic defense barrier and attenuating oxidative stress [165]. Butyrate also enhances the intestinal barrier by modulating the assembly of tight junctions (TJs) via AMP-activated protein kinase (AMPK) activation [166]. Feces of T2D subjects were relatively enriched with endotoxin-producing gram-negative bacteria (phyla Bacteroidetes and Proteobacteria), which suggested the role played by these phyla in T2D pathogenesis through an endotoxin-induced inflammatory response pathway [163]. In the liver, cholic acid and chenodeoxycholic acid constitute primary bile acids produced from cholesterol, and the gut microbiota transforms these primary bile acids into secondary bile acids [167]. In line with these facts, 6 weeks after the infusion of intestinal microbiota from lean subjects, an improvement in insulin sensitivity was noted in subjects with MetS [168]. Studies on the association between body composition and gut microbiota (Firmicutes, Bacteroidetes, Clostridium *leptum*, *Bacteroides, Bifidobacterium, Akkermansia muciniphila, Escherichia coli, and Faecalibacterium prausnitzii)* in type 2 diabetes using body composition of lean tissue index (LTI) and fat tissue index revealed that T2D with higher abundance of phylum Firmicutes and a higher ratio of phyla Firmicutes to Bacteroidetes (phyla *F*/*B* ratio) had higher LTI. This significant correlation between phyla *F*/*B* ratio and LTI was evident in type 2 DM with high body mass index and was independent of glycemic control or dipeptidyl peptidase-4 inhibitor usage, thus demonstrating the positive association of LTI with the abundance of phylum Firmicutes and the phyla *F*/*B* ratio in type 2 DM [169].

Iron Overload

There is no active mechanism for iron excretion in humans, and the amount of iron absorbed into the body is balanced by the iron lost by means of sloughing of intestinal mucosa and skin, as well as lesser amounts that are excreted in the urine and bile [170]. Iron overload is thus a risk factor for T2D [171], whereas its depletion has a protective effect against T2D.

The foremost evidences for this were obtained from studies related to pathologic iron overload disease conditions like hereditary hemochromatosis (HH) [172] and transfusional iron overload [173]. Both insulin deficiency and IR can con-

tribute to the T2D pathophysiology associated with HH [174, 175]. Individuals with HH have an inherent insulin secretory defect, making them highly prone to develop diabetes, especially when IR from an independent mechanism such as obesity intervenes [176]. HH individuals have extremely high ferritin levels (1000–10,000 ng/mL), and around 25–60% of them develop "secondary" T2D [177, 178]. Transfusional iron overload is usually seen in transfusion-dependent chronic hemolytic anemia such as β-thalassemia. Due to the numerous transfusions that are required to maintain adequate erythrocyte levels and the resultant increased iron absorption, these patients become iron-overloaded [179]. Individuals with β-thalassemia mostly develop IGT during the second decade of life, and a diabetes prevalence is reported among 6–14% of the patients [180, 181]. T2D is also prevalent among survivors of pediatric bone marrow transplantation [182] and allogeneic hematopoietic cell transplantation [183]. Some rare inherited diseases that cause diabetes such as Friedreich ataxia are associated with iron imbalance and mutations in the proteins involved in iron metabolism [184].

Positive associations between elevated body iron stores (measured as circulating ferritin) and the risk of T2D and of other IR states such as MetS, GDM, PCOS, and possibly CVD have been demonstrated [177, 185, 186]. Moderate increases in iron stores (lower than the levels found in HH subjects) were associated with increases in blood glucose and insulin levels. Furthermore, moderately increased body iron stores at baseline were associated with an elevated risk of developing T2D in future [178]. In a National Health and Nutrition Education Survey (NHANES), the odds ratios for newly diagnosed diabetes in individuals with higher serum ferritin levels were 4.94 for males and 3.61 for females [187]. A link has also been established between increased dietary iron intake (particularly heme iron) and the risk for T2D and GDM [188–191]. No significant association between dietary intakes of total iron, nonheme iron, and supplemental iron intake was found with the risk of T2DM, whereas heme iron intake showed a positive association after adjustment for potential confounders. Individuals who consume meat (a major source of heme iron) are thus reported to have more IR compared to vegetarians [177, 178].

Iron overload is also implicated in the pathogenesis of many diabetes-associated vascular complications including diabetic nephropathy (DNP) and CVD [188]. In individuals with DNP, an increased proximal tubular lysosomal iron concentration has been observed. In iron-loaded subjects with thalassemia, an early development and accelerated course of DNP is reported. Similarly, mutations for HH appeared to predict the development of DNP [192]. Iron has an adverse effect on the endothelium and accelerates the development of atherosclerosis. Elevations have been observed in ferritin gene expression during the course of atherosclerotic plaque formation [192, 193].

Multiple mechanisms have been proposed towards the association between iron and abnormal glucose metabolism, like β-cell dysfunction and IR, possibly mediated through oxidative stress [188, 194]. Being a redox-active transitional metal, excess iron is potentially hazardous. It catalyzes several cellular reactions that lead to the production of reactive oxygen species and thereby to an elevated oxidative stress, which is proposed to contribute to an increased risk of T2D. Pancreatic β-cells, due to their weak antioxidant defense system, are highly susceptible to oxidative damage, and thus iron deposition in these cells can result in impaired insulin secretion. In the muscle, iron overload may diminish glucose utilization, thereby leading to a shift from glucose to fatty acid oxidation, resulting in an increased IR. Increased substrate recycling to the liver may contribute to an elevated HGP. Iron may also impair the action of insulin and interfere with glucose uptake in adipocytes. Elevations in systemic inflammation may also modify iron metabolism. Inflammatory cytokines are found to induce the synthesis of ferritin [177, 178]. As iron influences the action of insulin, insulin also is in turn known to influence iron metabolism. Insulin plays a role in redistributing transferrin receptor (TfR) to the cell surface and thereby increasing the cellular uptake of iron in adipose tissue and the liver. Thus, in the IR states, inherent hyperinsulinemia leads to elevations in levels of the circulating soluble form of TfR (sTfR), a marker of iron status [177].

The potential benefit of iron depletion on insulin sensitivity and/or T2D has been evaluated by many. Phlebotomy enhanced insulin sensitivity and glycemia in normal as well as T2D subjects with elevated ferritin levels [177, 195]. In HH patients, phlebotomy and/or iron chelation therapy (to decrease body iron stores) improved their glycemic control, and 30–40% of them achieved either the elimination of oral diabetes therapy or a substantial decrease in dosage [196]. Blood donations reduce circulating ferritin levels, and frequent blood donors seem to have better insulin sensitivity than non-donors. An increased number of lifetime blood donations was found to be associated with a decreased prevalence of T2D [197]. Among T2D individuals who were negative for common HH but had increased serum ferritin concentration, bloodletting improved their insulin sensitivity and reduced their C-peptide levels [192].

Covid-19 and Type 2 diabetes

The importance of testing and treating diabetes has been overemphasized during the Covid pandemic.

The severity of Covid-19 is found to be increased in patients with uncontrolled diabetes mellitus and also in patients with new-onset hyperglycemia. There are multiple factors that can contribute to hyperglycemia in a Covid-

affected individual. Blood glucose is currently recognized as the fifth vital sign in all patients, irrespective of the previous history of diabetes [198]. The interaction of hyperglycemia with other risk factors might modulate immune and inflammatory responses, thus predisposing patients to severe Covid-19 and possible lethal outcomes. Angiotensin-converting enzyme 2 (ACE2), which is part of the renin–angiotensin–aldosterone system (RAAS), is the prime entry receptor for the SARS-CoV-2 virus, even though dipeptidyl peptidase 4 (DPP4) might also act as a binding target [199]. Potential pathogenic links between Covid-19 and diabetes include effects on glucose homeostasis, inflammation, altered immune status, and activation of the renin–angiotensin–aldosterone system (RAAS) [200]. Also, a known history of diabetes and a fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) before steroid treatment were recognized as independent predictors of mortality.

Conclusion

The alarming rise in the prevalence of type 2 diabetes due to obesity, reduced physical inactivity, and an aging population demands rigorous efforts to improve our understanding of the devastating disease and its prevention. Extensive research on the causality and pathophysiology of T2D has contributed to a better understanding of the overwhelming effects of T2D. From modest steps, with the identification of only two factors, defective insulin secretion and IR, we are now able to appreciate the complexity and heterogeneity of the role-players in the pathogenesis of T2D (see Fig. 9.4). It is likely that many more factors are yet to be unveiled. The complexity of T2D demands a multifaceted therapeutic approach, which combines pharmacological and non-pharmacological interventions in an individualized way. While investing efforts to address the underlying complications and the mod-

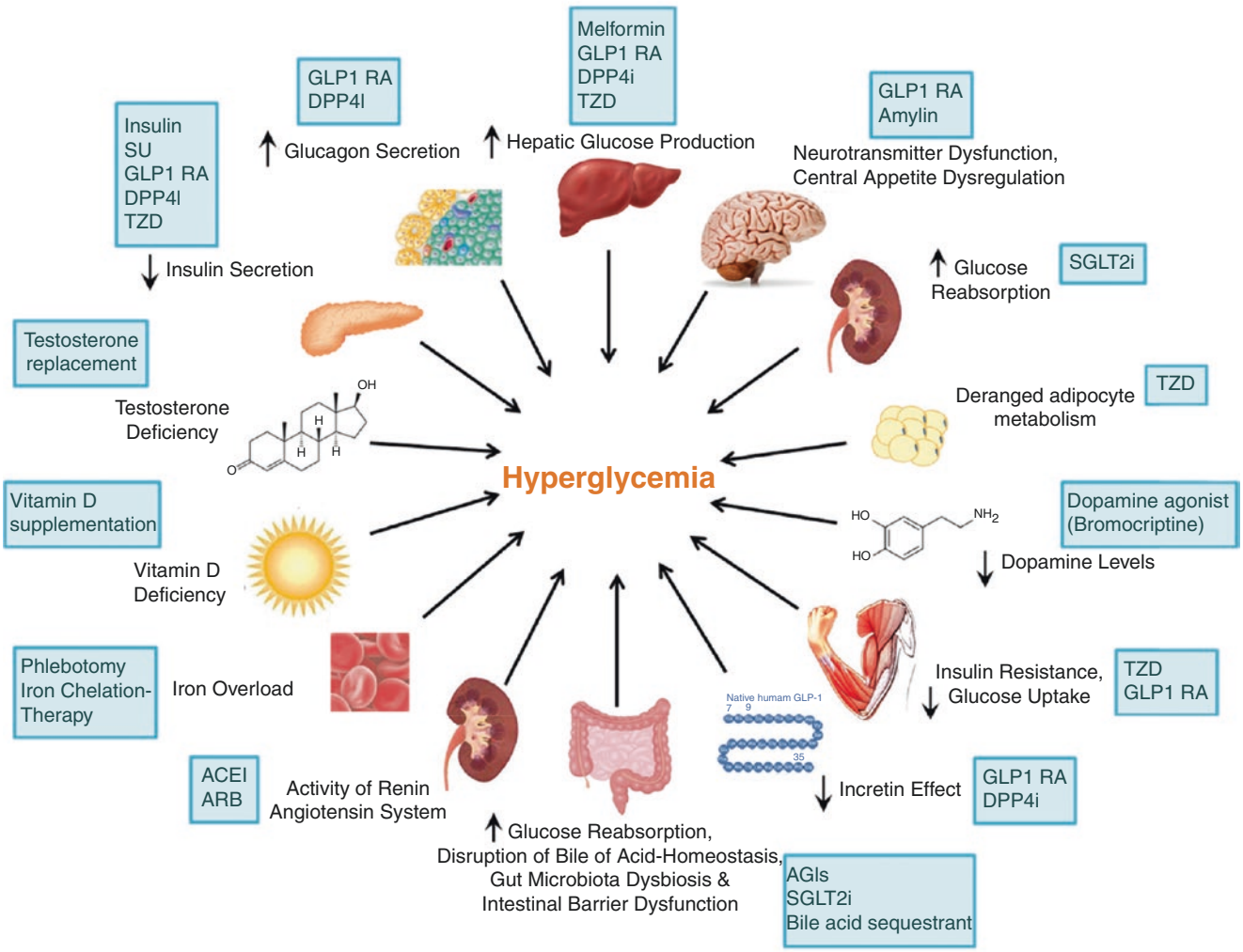

Fig. 9.4 Players in the pathophysiology of T2D

ifiable risk factors to prevent T2D, this knowledge will strengthen our views on the effective use of the existing therapies and allow us to explore and develop innovative solutions to tackle chronicity.

Multiple-Choice Questions

1. In the postabsorptive state, most of the glucose utilization occurs:
   (a) **In the muscle**
   (b) In the brain
   (c) In adipose tissue
   (d) In beta cells
   (e) In red cells
2. Regarding lipoprotein metabolism:
   (a) Insulin has not demonstrated effects
   (b) Insulin increases circulating VLDL levels
   (c) Insulin stimulates lipoprotein lipase in adipocytes, promotes lipolysis and removal of chylomicrons
   (d) **Insulin stimulates lipoprotein lipase in the vascular endothelium, reduces lipolysis and removal of chylomicrons**
   (e) Insulin increases triglyceride levels
3. In the event of hepatic insulin resistance:
   (a) Hepatic glucose production is suppressed by low fasting insulin levels
   (b) Hepatic glucose production initially continues but is suppressed as insulin levels increase
   (c) Hepatic glucose production is stable
   (d) **Hepatic glucose production continues even when fasting insulin levels are high**
   (e) Hepatic glucose production is suppressed
4. Postprandial hyperglycemia results:
   (a) From hepatic insulin resistance
   (b) **From peripheral tissue insulin resistance**
   (c) From beta-cell insulin resistance
   (d) From increased hepatic glucose production
   (e) From decreased transport of glucose in the central nervous system
5. The core physiological defects proposed in the triumvirate concept include the following, except:
   (a) **The central nervous system**
   (b) Pancreatic alpha-cells
   (c) Pancreatic beta-cells
   (d) The liver
   (e) Skeletal muscle
6. Individuals in the upper tertile of "normal" glucose tolerance:
   (a) Maintain 100% of beta-cell function
   (b) Have lost 20% of beta-cell function
   (c) **Have lost 50% of beta-cell function**
   (d) Have lost 70% of beta-cell function
   (e) Have lost 100% of beta-cell function
7. Amyloid deposits within the pancreas:
   (a) Have a protective effect on beta-cell function
   (b) Are crucial to initiating type 2 diabetes
   (c) **Are involved with disease progression**
   (d) Are associated with disease remission
   (e) Indicate glucose-toxicity
8. Insulin resistance
   (a) **Appears years before the onset of type 2 diabetes**
   (b) Is an unusual manifestation of type 2 diabetes
   (c) Is a late manifestation of type 2 diabetes
   (d) Occurs at the same time as beta-cell failure
   (e) Always evolve to type 2 diabetes
9. Hepatic gluconeogenesis is facilitated by:
   (a) The incretin effect
   (b) By overactivity of the beta-cells
   (c) By basal insulin secretion
   (d) By high levels of VLDL lipoproteins
   (e) **By high levels of free fatty acids**
10. In persons with type 2 diabetes, the largest impairment of glucose disposal occurs:
    (a) In the central nervous system
    (b) In adipose tissue
    (c) In the kidney
    (d) **In skeletal muscle**
    (e) In erythrocytes

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Genetic Determinants of Type 2 Diabetes

10

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Definition of Genetic Polymorphisms

The genetic information of modern man, or *Homo sapiens*, is kept along 23 pairs of chromosomes located in the nucleus of every diploid cell. Diploid is understood as the cells that have in their nucleus a double number of chromosomes, that is, two complete copies of the genomes inherited from the parents, which correspond to maternal and paternal alleles.

Sequencing studies have described that the human haploid genome is made up of approximately 3300 million pairs of bases (3300 Mb), of which approximately 25,000 genes have a coding function and, of these, only 8% (8000) have a known function and/or action mechanism [1].

Genes are considered the unit of genetic information that codes a functional product and as a unit of inheritance, which is distributed throughout the chromatids of the chromosomes in a specific position of DNA known as the locus. During the process of transcription, a copy of the DNA is made, which is known as the heterogeneous nuclear RNA, which proceeds to form mRNA, which codes for structural and functional proteins.

Approximately 99.9% of the DNA sequence is identical in humans; the remaining 0.01% represents genetic or allelic variations, also called SNPs. The presence of SNPs varies in different populations, which can explain evolution theories, migrations and even the ethnic origins of different populations. In addition, it offers information about the phenotypical diversity within the same species, which describes a proportion of relative susceptibility to certain diseases among individuals.

The Importance of Studying Genetic-Environmental Variant Interaction and Its Perspective in Clinical Application

There are various kinds of polymorphisms which are characterized by their presence or absence, their shape or size, the largest being insertions and deletions. In addition, there are other genetic variants known as repetitions of the copy number (CNV, copy number variation) and SNPs. Unlike mutations, SNPs are changes with a frequency greater than 1% of the population. If SNPs are characterized by a simple exchange of nucleotides of adenine, cytosine, thymine or guanine in the alleles, they are extremely important due to the fact that they are responsible for almost 90% of human phenotypical diversity. In 2008, for the first time, the "1000 Genomes Project" initiative was proposed to analyze the genetic material of 1000 people around the world and to study genetic variability. Finally, in 2015, the number of subjects analyzed reached 2500; the data suggested that in every healthy individual, there are around 150 variants that cause premature protein termination and another 30 implicated in the appearance of rare diseases. In addition, to the presence of more than 84 million SNPs in the human genome, they located between 100 and 300 pairs of bases throughout the genome [2, 3], generated by genetic recombination or missense (http://www.internationalgenome.org/data#download).

It has been reported that approximately 88% of the SNPs associated with disease are located in intronic and intergenic non-coding regions, which are found in areas not related to sequences that contain essential information for the expression of a gene [4]. The remaining 12% of the SNPs are called "coding", integrated into exonic areas, giving way, in the majority of

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cases, to proteins that can differ in their composition and biological functions. Also, exonic SNPs may be synonymous and not produce a change in amino acid or nonsynonymous and change the sequence of amino acids, which would alter the structure, conformation and shape of the protein. Due to the fact that SNPs are genetically stable, they are maintained for various generations and can act as true biological signals. Currently SNPs are considered ancestral risk or protector markers for diseases, from a clinical point of view. Nevertheless, their analysis is complex due to the fact that clinical phenotypes are the result of the interaction between the genotype and the exome that involves personal pathological backgrounds and unhealthy lifestyles, which contribute to the metabolic alteration present in T2D. Therefore the evaluation of the gene-environment correlation in cohorts will allow a better understanding and interpretation of the physiopathology of the genic behavior of complex metabolic diseases, which hold first place in global morbi-mortality. In addition, they will create useful tools for early detection, prevention and more effective treatment in order to reach adequate therapeutic goals [5].

Genome-Wide Association Studies (GWAS)

Identifying the genetic determinants associated with T2D has been a complex task due to the role that is also played by the environment in the development of the disease. Nevertheless, currently, there are various genetic markers distributed throughout the genome. Analysis of previously reported candidate genes has allowed confirmation of the association of the genes with the disease in various populations; however, replication is not always successful due to phenotypical variation and ancestry. GWAS is a method that bases its analysis on statistical and biological associations among various SNPs and phenotypes of diseases.

The rapid development of genotyping techniques and the reduction in costs have allowed for a greater number of GWAS. These studies use microarrays with more than 1,000,000 SNPs and have transformed research into the genetics of complex diseases, with diabetes being outstanding. GWAS are characterized by the possession of a greater power to discover variants with a modest effect, whose association is not previously known. The first studies confirmed the associations between T2D and various genetic variants located on *PPARG* genes, adding six new loci (*CDKAL1*, *HHEX*, *SLC30A8*, *IGF2BP2*, *CDKNA2A* and *FTO*). Typically, each copy of these susceptibility alleles increases the risk of suffering diabetes by 10–15% [6].

Initially, GWAS was performed on the European population and later on other populations from the African and American continents with different ethnic groups, which has contributed to the identification of a greater number of genes associated with T2D. Table 10.1 shows the association of

Table 10.1 Association of SNPs with susceptibility to developing T2D in a trans-ethnic meta-analysis that included thousands of cases and controls with the ancestry groups European, East Asian, South Asian, Mexican and Mexican American

			Alleles		Trans-ethnic meta-analysis	
Locus	Lead SNP	Chr	Risk	Other	*p*-value	Cochran's *Q p*-value
TCF7L2	rs7903146	10	T	C	7.8E−75	5.5E−04
PEPD	rs3786897	19	A	G	3.3E−04	5.5E−04
KLF14	rs13233731	7	G	A	7.0E−04	6.4E−04
CDKAL1	rs7756992	6	G	A	1.6E−26	2.6E−03
VPS26A	rs1802295	10	T	C	1.4E−03	4.4E−03
GCC1	rs6467136	7	G	A	2.0E−01	5.6E−03
TSPAN8	rs7955901	12	C	T	1.6E−03	6.1E−03
GCKR	rs780094	2	C	T	1.0E−05	8.7E−03
GRB14	rs3923113	2	A	C	1.5E−06	1.3E−02
BCAR1	rs7202877	16	T	G	5.7E−04	1.3E−02
ZFAND3	rs9470794	6	C	T	3.6E−03	1.4E−02
PSMD6	rs831571	3	C	T	3.7E−04	1.5E−02
CILP2	rs10401969	19	C	T	9.7E−03	2.0E−02
RASGRP1	rs7403531	15	T	C	1.5E−01	2.1E−02
RBMS1	rs7593730	2	C	T	4.7E−04	2.7E−02
TLE4	rs17791513	9	A	G	3.2E−08	3.0E−02
ZBED3	rs6878122	5	G	A	6.3E−05	3.1E−02
HHEX/IDE	rs1111875	10	C	T	3.2E−19	3.4E−02
CDC123	rs11257655	10	T	C	2.6E−09	4.3E−02
ARAP1 (CENTD2)	rs1552224	11	A	C	1.2E−07	5.5E−02
KCNQ1	rs163184	11	G	T	1.7E−14	5.8E−02
NOTCH2	rs10923931	1	T	G	1.7E−02	6.8E−02
JAZF1	rs849135	7	G	A	1.7E−09	6.9E−02
KCNJ11	rs5215	11	C	T	3.2E−11	7.2E−02
DGKB	rs17168486	7	T	C	3.4E−07	7.6E−02
THADA	rs10203174	2	C	T	4.8E−05	8.3E−02
KCNK16	rs1535500	6	T	G	7.5E−06	9.2E−02
ST64GAL1	rs16861329	3	C	T	8.5E−06	1.1E−01
MTNR1B	rs10830963	11	G	C	2.0E−07	1.2E−01
PTPRD	rs17584499	9	T	C	6.0E−01	1.2E−01
PROX1	rs2075423	1	G	T	2.2E−06	1.4E−01
HNF4A	rs4812829	20	A	G	4.6E−08	1.5E−01
GIPR	rs8108269	19	G	T	4.9E−06	1.5E−01
HMGA2	rs2261181	12	T	C	3.6E−08	1.8E−01
SPRY2	rs1359790	13	G	A	5.8E−06	2.2E−01
AP3S2	rs2028299	15	C	A	5.2E−07	2.4E−01
ADAMTS9	rs6795735	3	C	T	2.1E−04	2.5E−01
GCK	rs10278336	7	A	G	1.3E−01	2.6E−01
ZFAND6	rs11634397	15	G	A	1.4E−05	2.8E−01
FTO	rs9936385	16	C	T	1.2E−12	3.0E−01
GLIS3	rs7041847	9	A	G	5.4E−06	3.1E−01
CCND2	rs11063069	12	G	A	7.5E−04	3.2E−01
IGF2BP2	rs4402960	3	T	G	9.5E−18	3.3E−01
TMEM163	rs6723108	2	T	G	4.0E−01	3.3E−01
PPARG	rs1801282	3	C	G	5.7E−10	3.5E−01
HNF1B	rs4430796	17	G	A	8.9E−10	3.6E−01
PRC1	rs12899811	15	G	A	5.7E−07	3.9E−01

Table 10.1 (continued)

Locus	Lead SNP	Chr	Alleles		Trans-ethnic meta-analysis	
			Risk	Other	*p*-value	Cochran's *Q p*-value
CDKN2A/B	rs10811661	9	T	C	1.1E−27	3.9E−01
HNF1A	rs12427353	12	G	C	3.9E−06	3.9E−01
GRK5	rs10886471	10	C	T	6.1E−01	4.3E−01
ANK1	rs516946	8	C	T	1.5E−07	4.4E−01
SRR	rs391300	17	C	T	6.8E−01	5.1E−01
KLHDC5	rs10842994	12	C	T	7.9E−06	5.3E−01
TP53INP1	rs7845219	8	T	C	6.4E−08	5.4E−01
C2CD4A	rs7163757	15	C	T	3.6E−06	5.5E−01
BCL11A	rs243088	2	T	A	3.2E−06	5.5E−01
DUSP8	rs2334499	11	T	C	1.0E−03	5.6E−01
SLC30A8	rs3802177	8	G	A	1.8E−18	6.2E−01
WFS1	rs4458523	4	G	T	2.1E−09	6.2E−01
ANKRD55	rs459193	5	G	A	8.9E−04	6.7E−01
TLE1	rs2796441	9	G	A	1.6E−06	7.7E−01
IRS1	rs2943640	2	C	A	7.2E−09	7.9E−01
UBE2E2	rs7612463	3	C	A	6.7E−09	8.3E−01
HMG20A	rs7178572	15	G	A	1.5E−11	8.4E−01
ZMIZ1	rs12571751	10	A	G	2.4E−10	9.3E−01
ADCY5	rs11717195	3	T	C	2.2E−08	9.4E−01
MC4R	rs12970134	18	A	G	2.6E−08	9.5E−01
RND3	rs7560163	2	C	G	4.7E−01	9.9E−01
MAEA	rs6815464	4	C	G	4.4E−04	N/A

Taken from [7]

various SNPs with susceptibility to developing T2D in a trans-ethnic meta-analysis that included thousands of cases and controls with the ancestry groups European, East Asian, South Asian, Mexican and Mexican American [7]. To date, there are more than 80 SNPs, among which are variants in genes *WFS1, HNF1A, HNF1B, IRS1* and *MTNR1B*. The importance of the genetic component of T2D is clear when a concordance of 70–90% of the disease is observed between identical twins.

GWAS has allowed us to understand with greater precision the physiopathology of T2D in order to establish better opportunities for treatment, diagnosis and patient monitoring. From a genetic viewpoint, T2D is a multifactorial disease where the phenotype of a group of genes is modulated by environmental factors. The action mechanisms involved in the majority of signs associated with T2D offered by the GWAS are involved in a reduction in the secretion of insulin (be it due to dysfunction of the pancreatic beta cells or through reduction of cellular mass) or insulin resistance (associated with obesity). In conclusion, GWAS has offered important knowledge of the genetic variants most associated with T2D in the world [8]. Another focus for complex diseases is whole-exome sequencing. This has been successful in the study of low-frequency variants.

The Importance of Ancestry in Association Studies

It is known that in populations native to the American continent, there was a process of miscegenation that took place when the Amerindians and Europeans met in the New World five centuries ago. The latest studies show that the genetic composition is different in each country, and within the same country there are regional differences. For example, in Mexico, it has been shown that Mexico City has the following percentages: 65% Native Americans, 30% Europeans and 5% Africans, while in Monterrey City, N.L., the percentage was 56% Native Americans, 38% Europeans and 6% Africans [9, 10]. Even in Mexico City, there are variations in the proportions of ancestry when we compare the IMSS vs. INMEGEN studies [11]. Recently, a high prevalence of Amerindian ancestry was reported in the Montaña region of the State of Guerrero, reaching 80% Amerindian [12].

In Mexico, there is a very high degree of stratification, where the differences in allele frequencies between groups and controls can lead to false associations [9]. The Admixture Mapping method avoids these false associations and requires markers that may be informative concerning ancestry, that is, those for which allele frequencies differ between mixed populations. With this method, data is combined from all the markers to obtain information about the ancestral alleles of each marker locus and then the association of the disease with ancestral background. We can combine the information from multiple markers in a multivariate analysis to obtain information about the ancestral alleles of each locus of each individual in the admixture.

The importance of this chapter is to describe the most important genetic variants associated with T2D (Table 10.1). For more information about frequencies, haplotypes, etc., consult http://www.internationalgenome.org/, and variants associated with diseases like T2D are listed in the link to the ENCODE Project at https://www.genome.gov/10005107/.

Genes Associated to T2D

TCF7L2 Variants Gene

The *TCF7L2* gene has clinical relevance because it is implicated in a wide variety of signals, insulin resistance and T2D, specifically the variant rs7903146 in European populations, later also in Latin peoples. In 2006, the first gene implicated in susceptibility to T2D was identified through microsatellite markers, being identified without previous biological knowledge and with an important power of association, and which was named *transcription factor 7-like 2 gene* (*TCF7L2*; *TCF4*). It is known that *TCF7L2* is a transcription factor that influences the transcription of various

genes, thus exercising a great variety of functions within the cell. This transcription factor is a member of the signaling pathways of Wingless Int (WNT), located on chromosome 10q25. Stimulation of the WNT pathway goes along with the association of β-catenin with BCL9 and its translocation to the nucleus associated with *TCF7L2,* which results in the activation of WNT target genes, specifically in the repression of the synthesis of proglucagon in enteroendocrine cells. The non-coding area contains cis-regulatory elements that lead to the expression of *TCF7L2* in various tissues involved in the homeostasis of glucose, which suggests that the variants are probably regulating the expression of this gene. The T risk allele of *rs7903146* presents greater expression in the pancreas than the C protector allele [13]. Markers located on intron 3, *DG10S478*, and SNPs *rs12255372* (allele G > T) and *rs7903146* (allele C > T) were the first markers associated with T2D in individuals in Iceland [14]. Later, this association was replicated in various populations around the world, so this gene susceptible to T2D has become the most important worldwide. In the European population, each copy of the susceptibility allele increases the risk of developing T2D 1.4–1.5 times. In the Mexican population, the risk is 1.78 for each copy of the T allele for rs12255372, after adjusting for ancestral markers [15].

Lyssenko et al. showed that the risk given by the T allele of *rs7903146* is associated with a lack of insulin secretion, the effect of incretin and increase in the production of hepatic glucose. In addition, a cohort in Bosnia and another in Malmö showed how diabetes-free survival is greater in individuals with genotype CC than in individuals with CT/TT del *rs7903146* [12].

Variants of Genes *ABCC8* and *KCNJ11*

Genes of the family *ABCC8* (union cassette ATP, subfamily C, member 8; SUR1) and *KCNJ11* (inwardly rectifying potassium channel, subfamily J, member 11; KIR 6.2) are located on chromosome 11p15.1; it has been observed that both are expressed in beta cells, and it has been reported that various polymorphism versions on these genes associate with insulin secretion disorders [16].

It has been noted that carriers of the variant *p.Arg1420His* of gene *ABCC8* have twice the risk of developing T2D, mainly among Pima Indians, although this also applies to subjects with mostly Native American ancestry [17].

In Europeans, the association has been reported with variant *KCNJ11 E23K* (OR 1.23), but not with *ABCC8* [15]. Nevertheless, between these two genes, there is a high degree of linkage disequilibrium (LD), which makes it harder to identify the variant causing the risk of the disease [18].

Variants of Gene *CAPN10*

Calpain is a cysteine protease which participates in various functions such as apoptosis, exocytosis, mitochondrial metabolism and remodeling of the cytoskeleton and insulin secretion. Its expression is very high in metabolically important organs such as the heart, liver, pancreas islets and muscle. Known as the common gene in diabetes, it is located on chromosome 2q37.3, formed by 15 exons and showing 8 isoforms [19]. The most recent meta-analysis showed that the C allele of *rs2975760* of *CAPN10* was the best associated with increased risk of T2D [20]. However, an analysis by haplotypes showed that individuals with haplotype 1121/1121 for SNPs -44, -43, -19, or -63 presented twice the risk of T2D than only SNP-*43* [21]. This haplotype is not associated with other populations, which means that the genetic structure of each population is important and should be considered, as in other SNPs.

Variants of *PPARγ* Gene (Peroxisome Proliferator-Activated Receptor Gamma)

PPAR is a protein member of a superfamily of nuclear receptors which has a weight of approximately 56 kDa. PPAR affects mechanisms present in the control of steroid hormones, glucocorticoids, or thyroxine, retinoic acid and vitamin D, but mainly acts in the regulation of the expression of specific genes through a mechanism that is common to members of the nuclear receptor superfamily. It has been reported that the PPAR family is comprised of various subtypes known as PPARα, PPARβ/δ and PPARγ. This latter is coded by three different genes: *PPARγ1, PPARγ2* and *PPARγ3*. The main function is the regulation of genes that participate in lipid and glucose metabolism. Variants of *PPARγ2* in 3p25 are only expressed in adipose tissue and regulate the differentiation, storage of lipids and control of the transcription of various genes implicated in metabolism, and they also participate in insulin sensitivity [22]. Various studies have shown that PPAR antagonists improve hyperlipidemia and glucose levels.

Pro12Ala (*rs1801282*) has been associated with T2D in different populations. *Pro12Ala* has a prevalence of 12% in the Caucasian population, 10% in Native Americans and 1% in Chinese. This change in amino acid near the extreme amino terminal (NH2-terminus) modulates the transcriptional activity. Alanine favors the formation of alpha-helix, which does not occur with proline, which forms alanine isoforms, and stimulates deficiency in the target genes of the gene, carrying to the individual carriers a lesser accumulation of adipose tissue. In the latest meta-analysis, an OR of 0.86 was calculated, but unfortunately, the majority of the

population at the global level carries the allele Pro12, which generates a high risk of T2D [22].

On the other hand, it has been noted that *PPARγ* has been highly studied due to the fact that its ligands interact with thiazolidinediones, drugs used in the treatment of T2D. The effects of ligands of *PPARγ* are diverse, but the total effect is improvement in insulin sensitivity, in addition to regulation of other genes that have functions in glucose homeostasis and adipocyte differentiation.

Variants of the *CDKN2A/B* Gene

CDKN2A/B gene is located in region 9p21 and codifies for a protein p16, which has the function of inhibiting cyclin-dependent kinases p16 (INK4A) and p15 (INK4B), coded by the gene *CDKN2A* and a long non-coding RNA known as *ANRIL* (*CDKN2B-AS*) [23]. It participates in the cellular cycle and helps maintain pancreatic beta cell mass, but the mechanism by which *CDKN2A/B* influences diabetes risk is not yet clear. The risk allele of marker *rs10811661* has been associated with reduced insulin secretion in the European population [24], while genes *MTNR1B, TCF7L2* and *KCNJ11* are associated with the dysfunction of β cells; both pathways are related to the reduction of insulin secretion [16].

Variants of the *FTO* Gene

Association of the fat mass and obesity-associated (*FTO)* gene with obesity was first reported in a European GWAS study performed in individuals with T2D [25]. The power of association of the variant of the *FTO* gene with T2D was lost when correcting for body mass index (BMI), which suggested that susceptibility was being measured through obesity. Other studies have reported that the association between the variant and the risk of T2D is maintained after adjusting for BMI. It appears that the main cause of the variability of results is related to the time when BMI was measured. The association has been demonstrated before the development of T2D when BMI is more elevated and is reduced or lost with the greater time of evolution of the disease.

Studies confirm the association between the variant *rs9939609 (T/A)* of *FTO* and obesity as the main risk factor for developing T2D. In other populations, such as the Mexican, the association is not as evident, particularly in children [26]. European homozygote populations for the risk allele (AA) of *rs9939609* have 1.7 times the risk of developing obesity and on average have 3 kg more weight than the average population. Some studies have tried to identify the mechanism by which this association exists. In a metabolomic focus, metabolites have been identified, such as valine amino acid, a hexose, and other metabolites relevant to the phosphatidylcholine pathway. The alteration of valine metabolism leads to the accumulation of branched-chain amino acids in relation to the risk allele of *FTO*. The branched-chain amino acids and their derivatives seem to be an early manifestation of insulin resistance, probably via *mTOR/S6K1* kinase, which results in the phosphorylation of various residues of serine in the substrate of the insulin receptor (IRS-1). Metabolites of phosphatidylcholine are associated with apolipoprotein B, and it has been demonstrated that the risk allele of *FTO* is associated with the particles that form part apolipoprotein B.

Variants of the IRS-1 Gene

The molecules of IRS are important mediators in the signaling of insulin, in addition to playing an important role in the metabolism, growth and survival of the cell. The IRS family is formed by four members, IRS-1 to IRS-4, each presenting a different tissue distribution and therefore a different expression. IRS-1 and IRS-2 are key for insulin action and glucose homeostasis. IRS-1 is coded on chromosome 2q36.3. Polymorphism *Gly972Arg* of *IRS-1* has been most associated with the development of T2D. The union of insulin to its active phosphorylated receptor *IRS-1* phosphorylates tyrosine residues, serine and threonine (Ser/Thr), which join and activate PI3K, which contains the subunit p85, and p110 phosphorylates PI, which allows it to join with akt and PDK1. The phosphorylation of tyrosine residues accompanies the mobilization of glucose transporters (GLUT 4) that mediate the internalization of glucose. However, when the serines or threonines are phosphorylated, it leads to an accelerated degradation of the IRS protein, which generates an alteration in insulin signaling, insulin resistance and a decrease in the translocation of GLUT4.

As mentioned earlier, the polymorphism *Gly972Arg* has been the most reported in studies of association with T2D, in combination with environmental factors such as diet, age and physical activity. Like other genes and depending on the population, important associations have also been reported (such as in Europeans), weak ones as with the Japanese, or absence of, as with the Pimas [27]. In the Mexican population, variant *Arg* has been observed in 2.6% of controls and 7.9% of cases [28].

Variant of the Gene Hepatocyte Nuclear Factor 1-Alpha (*HNF1A)*

HNF1A is coded on chromosome 12q24.31. The protein joins the inverted palindrome 5′-GTTAATNATTAAC-3′ for the activation and regulation of gene expression, mainly in

the cells of the pancreatic islets and the liver. Some variants of the gene have been found to be associated with maturity-onset diabetes of the young 3 (MODY3). Through the study of exome sequencing, the variant pE508K has been identified and associated with T2D. This variant generates a reduction in the function of the protein, unlike MODY3 diabetes, where the function is almost lost. The mechanism related to the affinity of the protein for joining DNA sequences does not appear to be altered. It seems the reduction in activity occurs mainly through a reduction in expression, and the protein shows altered localization in the nucleus.

The effect of the variant on European populations is very high, with results similar to those of two studies on the Latin population. Carriers of the variant have up to a fivefold increased prevalence of T2D. Interesting from a clinical viewpoint, carriers of the variant respond better to treatment with sulfonylureas than with metformin, the drug of choice in the treatment of T2D [29].

Variant of the Gene *Solute Carrier Family 30 Member 8 (SLC30A8)*

This transporter, coded on chromosome 8q24.11 and expressed importantly in the Isles of Langerhans in the pancreas, participates in the packaging of proinsulin in secretory granules and liberation. These processes require the presence of the ions Zn^{2+} and Ca^{2+}, which form complexes with proinsulin. The ions of Zn^{2+} are transported by transporter 8, which is found in abundance in the pancreas beta cells and also located in alpha cells and participates in the liberation of glucagon. GWAS have associated the gene with susceptibility to developing T2D. A recent study showed that the marker associated with the greatest frequency in the European, Asian and African populations is rs13266634 [30]. However, other authors have not found this gene to be associated with T2D [31].

Other Variants Associated to Insulin Resistance and Dyslipidemias

Variant *R230C* of gene *ABCA1* of the HDL receptor participates in the reverse transport of cholesterol, which is associated with early-onset diabetes and obesity, particularly in the Mexican population, with values of $p = 10^{-6}$ [11]. Also, in the Japanese population, the presence of a haplotype with an OR of 2.59 has been reported to be associated with T2D [32].

In a meta-analysis of Mexican and Mexican-American samples to characterize genes associated with T2D in Hispanics, the following genes were identified, with values of $<10^{-5}$: gene *ATP2B2*, located on chromosome 3; *UNC5C* on chromosome 4 and *PIWIL4* on chromosome 11, in addition to three independent intergenic regions located on chromosome 10 and an expressed sequence tag (*EST*) sequence located near the area of gene *RXRA* on chromosome 9. Upon adjusting for BMI, two additional groups of markers were observed, one in the intergenic area of chromosome 20 and the other within genes *C22orf30/DEPDC5*, located on chromosome 22. This meta-analysis showed SNPs with a high level of significance in ten genomic areas. In addition, two additional regions were identified when BMI was incorporated, in particular an intronic variant of the *ANK2* gene and two intronic variants of the *MCPH* gene [33, 34]. Other population studies have identified genes such as *HNF1A*, *KCNQ1* and *PTPRD*. Also, two other genes identified, *CSMD1* and *ANK2*, were relevant due to their functionality in metabolic regulation. Other regions associated with T2D showed statistical significance, including the *CDKN2A/CDKN2B* and *IGF2BP2* genes.

Biological Validation Studies

After the identification of the genes associated with a disease, what is sought is to know their biological function, so that the genes mentioned above have been studied for their expression in adipose tissue, skeletal muscle, and lymphoblast cell lines. One of the most significant signals of SNP *rs202983*, located within the *CIT* gene (chromosome 12), showed an important effect on the regulation of gene *WFS1*. It has been documented that mutations in the *WFS1* gene cause monogenic diabetes and common variants of this gene have been associated with T2D. Lineal regression analysis of these genetic markers with five parameters (BMI, total cholesterol, HDL-C, LDL-C and triglycerides) showed values of the association at the genomic level in polymorphisms near the *APOA5* gene, which is located on chromosome 11. The variant *rs964184* showed the lowest value at $p = 2.3 \times 10^{-9}$. Other variants of interest are those of the *SYNE1* gene, which is found on chromosome 6, for triglycerides (*rs998147*, $p = 5.3 \times 10^{-7}$) and an area near the *MAD2L1* gene on chromosome 4 for HDL-C (*rs4568220*, $p = 7.1 \times 10^{-7}$) [33, 34].

Conclusions

T2D is a complex disease that presents differences in prevalence between populations. Epidemiological data indicate that the risk of suffering the disease is higher in Amerindian populations than those of European origin. There is evidence of the influence of genetic factors in populations; to date, over 80 loci associated with T2D have been identified, which do not always replicate among populations. Analysis by admixture mapping has been specifically designed to identify genes involved in complex diseases that show differences

in prevalence among populations. Given the history of miscegenation in the Mexican population, admixture mapping is an ideal method for identifying the genetic factors that increase the risk of suffering from T2D. The first GWAS performed in patients with T2D in Mexico showed that less than 10% of the 46 candidate genes reported in 2011 in the European population were found to be associated with our population. These populations are characterized mainly by low levels of HDL-C, high levels of LDL-C and elevated triglycerides. The genetic factors most associated with these alterations have been variants of *ZNF259/APOA5* genes, such as rs964184, associated with triglycerides, rs2367970 of the same gene, and rs2472386 of *ABCA1* gene, associated with HDL.

It is a priority to establish the genetic history of the Mexican in order to have risk markers for developing T2D, markers associated with complications and metabolic disorders, conditions very evident in our population thanks to current lifestyles.

Multiple-Choice Questions

1. A gene is considered to be:
   (a) A sequence of nitrogenated bases
   (b) **The unit of genetic and inherited information**
   (c) The chromatid unit that forms chromosomes
   (d) A sequence of nucleosides
   (e) Triplets of bases
2. What percentage of the DNA sequence is identical among humans?
   (a) **99.9**
   (b) 98.0
   (c) 95.0
   (d) 98.5
   (e) 99.0
3. The main difference between a mutation and an SNP is:
   (a) A mutation is lethal and an SNP is not
   (b) In mutation, there is a change in various bases
   (c) SNPs occur only in introns
   (d) **The frequency of an SNP is greater than 1%**
   (e) An SNP is presented at any stage of life
4. All are characteristics of SNPs except:
   (a) They are generally bi-allelic
   (b) They are presented throughout the structure of the gene
   (c) **They are only present in exons and introns**
   (d) They are inherited
   (e) They allow the identification of an individual
5. The gene most frequently associated with T2D worldwide is:
   (a) *IRS-1*
   (b) *CAPN10*
   (c) ***TCF7L2***
   (d) *PPARg*
   (e) *FTO*
6. Which is the action mechanism of variant rs1801282 of the gene *PPARγ*?
   (a) **Transcriptional modulation of the change of alanine**
   (b) Oxidation of free fatty acids
   (c) Transcriptional modulation of the signaling pathways of TZD
   (d) All of the above
   (e) None of the above
7. What is the main problem with the low replication of the association of obesity with T2D of the various genetic variants of the gene *FTO* upon analyzing it in different populations?
   (a) The loss of statistical power in meta-analysis
   (b) The ancestry of various populations
   (c) The time of evolution of the disease and the difficulty in performing metabolomics studies
   (d) **All of the above**
   (e) None of the above
8. Why is it important to determine the genetic component of metabolic diseases?
   (a) To identify risk or protector markers associated with the disease
   (b) To perform studies in metabolomics
   (c) **All of the above**
   (d) None of the above
9. What is the function of the gene *CAPN10*?
   (a) Participate in apoptosis, exocytosis, mitochondrial metabolism and remodeling of the cytoskeleton
   (b) The gene codes for calpain-10, an atypical cysteine protease that participates in the mechanism of insulin secretion
   (c) Participate in the oxidative use of glucose for skeletal muscle
   (d) **All of the above**
   (e) None of the above
10. Characteristics of gene *SLC30A8* include:
    (a) The transporter is coded on chromosome 8q24.11. It is expressed at a high level in the pancreas, particularly in the islets of Langerhans
    (b) It participates mainly in the packaging of proinsulin in secretory granules, the hepatic liberation and the elimination of insulin
    (c) It processes require the presence of ions Zn2+ and Ca2+, which form complexes with proinsulin
    (d) **All of the above**
    (e) None of the above

Glossary[1]

Ancestry The term may refer to the geographical origin of populations, for example, "individuals of European ancestry", or the line of heritage or descent of a group.

Diabetes Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels (American Diabetes Association).

Genetic marker A gene or (a fragment of) DNA sequence having a known location on a chromosome has an easily identifiable phenotype and an inheritance pattern that can be followed. Genetic markers act as chromosomal landmarks. They are used to trace or identify a specific region of a gene (especially one that is associated with an inherited disease) on a chromosome. They are also used to determine a linkage group or a recombination event.

Genome-Wide Association Study (GWAS) GWAS is a relatively new way to identify genes involved in human disease. This method searches the genome for small variations, called single nucleotide polymorphisms, or SNPs (pronounced "snips"), that occur more frequently in people with a particular disease than in people without the disease. Each study can look at hundreds or thousands of SNPs at the same time. Researchers use data from this type of study to pinpoint genes that may contribute to a person's risk of developing a certain disease.

Microarrays A microarray is a hybridization of a nucleic acid sample (target) with a very large set of oligonucleotide probes, which are attached to a solid support, to determine sequence or to detect variations in a gene sequence or expression or for gene mapping.

Single nucleotide polymorphisms (SNPs) SNPs are the most common type of genetic variation among people. Each SNP represents a difference in a single DNA building block, called a nucleotide. For example, an SNP may replace the nucleotide cytosine (C) with the nucleotide thymine (T) in a certain stretch of DNA.

[1]Some definitions are found on the page: https://ghr.nlm.nih.gov/.

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Gene Expression Modifications in Type 2 Diabetes

11

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Objectives

- Understand changes in gene expression that underlie the phenotype of T2D.
- Review the deregulation of inflammation, oxidative phosphorylation, carbohydrate, and lipid metabolism and mitochondrial function in four key organs involved in the development of T2D.
- Discuss the emerging role of microRNAs as local and distant regulatory molecules in T2D.

Introduction

The pathogenesis of type 2 diabetes (T2D) is not completely understood. It has been shown that environmental factors such as obesity, physical inactivity, unhealthy diet, and aging, in addition to genetic factors, play important roles in the genesis of T2D. The evolution of the technology in genomic analysis has made possible to find T2D susceptibility genes using genome-wide association study (GWAS) approaches. To date, more than 250 genomic regions have been identified related to T2D susceptibility or T2D-related glycemic traits [1]. Many of these loci have been associated with impaired β-cell function and insulin secretion. However, T2D is a complex metabolic disorder and is clear that several genes play important roles in this polygenic disease. It is not completely understood how those genomic variants (SNPs) are associated with T2D, if they are involved in the pathogenesis of the disease or act simply like risk markers. Only about 10% of the total variance of T2D is explained by the common variants identified by GWAS, and interestingly, most of the identified variants (>85%) fall in noncoding regions of the genome. This finding highlights their potential role in gene regulation.

Adipose Tissue

The participation of adipose tissue in the development of insulin resistance and T2D is tightly linked to two distinct groups of cells: adipocytes and immune cells. Adipose tissue has been recognized as an organ whose function is not limited to the sole storage of fat but has endocrine functions as well. The complex and still not-well-understood communication between cells during obesity triggers changes that end up with alterations in glucose homeostasis. These modifications are accompanied by the release of several signaling molecules such as adipokines and cytokines that can travel through the blood stream allowing them to reach local and distant organs where they exert their effects. Among an ample range of effects, these molecules may be able to modulate cell signaling and regulate expression of single or most often groups of genes in response to certain stimuli.

One of the most recognized molecules expressed differentially between lean and obese people is adiponectin. The concentration of this protein in circulation is inversely proportional to the body mass index (BMI). Furthermore, it has been reported that adiponectin gene expression is downregulated in obesity due to DNA hypermethylation of a region in its promoter [2]. This regulation is mediated by the DNA methyltransferase 1 (DNMT1) whose expression is elevated in adipocytes of obese individuals. Other studies have indicated that the leptin gene (its product has been classified as an adipokine which increases in concentration in obesity) may be regulated by DNA methylation [3]. In addition, protein-DNA affinity studies have identified the transcription factor *FOSL2* as an important regulator of *LEP* [4]. Leptin is a hormone that inhibits food intake and stimulates energy expenditure in lean individuals, but its function is lost or

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decreased in obesity where an increase in concentration tries to compensate for the development of leptin resistance. However, this increase in leptin levels generally does not improve obesity. The same pattern of expression has been observed with resistin which is a hormone that can cause insulin resistance and decrease adipocyte differentiation. The transcriptional regulation of this gene is related to the transcription factor FOXO1. The non-phosphorylated, active form of FOXO1 can activate the resistin promoter by binding to two regions upstream of the transcription start site (−1539 to −1366 bp and −1016 to −835 bp) [5].

There are a number of other genes whose expression is modified in obesity. For example, Hoggard et al. [6] performed a study in which they compared the gene expression between visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) which was obtained from obese individual. They found 22 genes that showed gene expression differences equal or greater than 5× in omental adipose tissue compared with SAT. Three of them codify secreted proteins (*GREM1*, *PTN*, and *SLPI*), but their function in adipose tissue has not been completely elucidated. However, recent data indicates that *GREM1* blocks *BMP4* which in turn decreases the expression of *PPARγ* and *C/EBPα*. These two transcription factors are key regulators in adipocyte differentiation. Thus, impairment of adipocyte differentiation in subject with fat-rich diets promotes the storage of excess of energy in enlarged adipocytes. Hypertrohy of adipose tissue is generally viewed as more negative than hyperplasia [7]. Indeed, it has been observed that adipose tissue hypertrophy is more frequent in diabetic subjects compared to nondiabetic subjects [8]. Regarding the *PTN* gene, one association study has found that the SNP rs161339 near this gene is associated with BMI [9]. PTN is able to induce the production of inflammatory cytokines; thus, it may be involved in the inflammatory response classically observed in obesity [6]. Recently, it has been reported that PTN and ADAMS1 inhibit the initiation of adipocyte differentiation which may further contribute to adipose tissue impairment [10]. The third differentially expressed gene, *SLPI*, codifies a protein with anti-inflammatory properties which may be produced to counteract the obesity-associated adipose tissue inflammation. This is supported by reports showing a positive association between circulating levels of SLPI and progression of metabolic dysfunction [11].

Other studies have shown that the genes *CIDEC/FSP27* (whose gene expression correlated with insulin sensitivity) and *PLIN1* (its dephosphorylated form inhibits lipolysis) are mainly expressed in the SAT and their levels in the VAT are negatively regulated by BMI, fat in depots, homeostatic model assessment (HOMA), and fasting glucose and are positively associated with genes that play a role in adipogenesis such as *PPARγ*, *GLUT4*, *FASN*, and *ACACA* and mitochondria biogenesis such as *PPARGC1A*, *PPARGC1B*, *TFAM*, and *MT-CO3* [12]. It has been demonstrated that TNF-α, a proinflammatory molecule usually found in obesity, decreases the expression of *CIDEC* by modifying the activation of the transcription factor PPARγ [13].

A study in subcutaneous adipose tissue from postmenopausal woman following a weight loss regime for 6 months indicates that a greater weight loss is associated with a decrease in 17b-hydroxysteroid dehydrogenase-1 (*HSD17B1*) and leptin (*LEP*) expression and marginally significant increased expression of estrogen receptor-1 (*ESR1*) and insulin-like growth factor-binding protein-3 (*IGFBP3*) [14]. HSD17B1 is an important component of the estrogen metabolism pathway because it catalyzes the conversion of less active estrone to estradiol [14]. Other pathways that were regulated during weight loss in postmenopausal woman were the mTOR and IGF-1 signaling pathway [14].

Changes in the expression of transcription factors during obesity and T2D excerpt broad effects in the cells since a single transcription factor is able to regulate several genes. However, due to its broad effect, it is sometimes challenging to fully understand its functions. For example, in adipogenesis, the expression of the transcription factor MAFB is upregulated. It increases with BMI in WAT and correlated with adverse metabolic features such as proinflammatory gene expression in adipocytes and macrophages of the adipose tissue. Weight loss decreases its expression [15]. However, these results do not agree with observations in mice where deficiency of this transcription factor lead to increased body fat due to larger adipocyte size and serum cholesterol levels. Possibly, this association is mediated by a reduction in AIM (apoptosis inhibitor of macrophages), which is an inhibitor of lipogenesis in adipocytes [16]. Another transcription factor which is regulated by hypoxic conditions in obesity is the HIF1. Previous reports showed that HIF1 inactivation in the adipose tissue reduced obesity and insulin resistance. These results point to this transcription factor as a potential therapeutic target to treat T2D and obesity. Other transcription factors that are regulated in obesity are PPARγ and C/EBPα; both are important regulators of adipocyte differentiation and inflammation.

It is well established that low-grade chronic inflammation is a hallmark of obesity and T2D. However, the signals that trigger the inflammation in the adipose tissue are not well understood, but one molecule that has shown a great capacity to elevate expression levels of chemokines and cytokines in subcutaneous adipose tissue is the nutrient-induced intestinal hormone glucose-dependent insulinotropic peptide (GIP). Reports indicate that GIP may be involved in the crosstalk of adipocytes and macrophages by the stimulation of the GIP receptor in monocytes and the increase of *MCP-1* mRNA expression [17]. Other genes whose expression was elevated were *MCP-2*, *IL-6*, *IL-6R*, and *TNF-α* [17, 18]. This observa-

tion was confirmed in co-cultures of 3T3L1-adipocytes and RAW 264.7 macrophages but not in isolated cell lines which further supports the hypothesis of a crosstalk between macrophages and adipocytes [17]. Expression of IL-6 and its receptor in subcutaneous adipose tissue (SAT) is positively modulated by obesity and correlates with the expression of *CD11b* (subunit of a complex involved in leukocyte adhesion and migration), *CD163* (marker of the monocyte/macrophage lineage), *TNF-a*, *MCP-1*, and *IP-10* (or *CXCL10*) (it as a role in chemoattraction of immune cells in response to IFN-γ) [18]. Adipose tissue accounts for the expression of approximately 30% of systemic IL-6 [19]. Higher concentration is associated with insulin resistance and T2D development [19].

Another molecule that has been demonstrated that is able to positively regulate the expression of inflammatory genes such as *TNF*, *IL6*, *STAMP2*, *LBP*, *MCP1*, and *NF-κB* in adipose tissue is *DBC1* [20]. Particularly, regulation of *NF-κB* is mediated through the interaction of DBC1 with sirtuin 1 and inhibition of its deacetylase activity [21]. Decrease in sirtuin 1 action is also associated with macrophage recruitment in adipose tissue [21]. In humans, expression of *DBC1* is associated with adipose tissue senescence in morbid obese subjects [20]. Other inflammation-related genes expressed in adipocytes of obese patients are part of the NOD-like receptor pathway which has been identified as one group of genes associated with inflammation in adipose tissue. NOD-like receptors are intracellular sensors of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) which regulate caspase-1-mediated IL-1β secretion. Particularly, it has been reported that the expression of *NLRP3* and *PYCARD* (two important proteins required for the NLRP3 inflammasome activity) and the class II major histocompatibility complex (MHCII) correlate with adiposity phenotypes [22]. Activation of the NLRP3 inflammasome in hypertrophic adipocytes may be partially responsible of the adipocyte death by pyrosis which is an inflammation-programmed cell death which is observed in adipose tissue of obese individuals. The important role of NLRP3 in the development of T2D becomes clear in experiments where attenuation of the NLRP3 inflammasome was performed. The results showed a delay in the progression of diabetes, improved hyperglycemia, insulin signaling, and attenuated IL-1b secretion [23, 24]. When NLRP3 is not present, a reduction in the expression of other proinflammatory genes and the chemokine *CCL2*, *MCP-1*, and its receptor *CCR2*, which play an important role in macrophage chemotaxis, was observed [25]. On the other hand, recent findings point to an important role of MHCII in the CD4(+) T-cell activation and induction of IFNγ-dependent adipocyte IL-1β secretion which results in a diet-induced early insulin resistance in adipose tissue [26–28]. Interestingly, expression of MHCII is higher in hypertrophic adipocytes which are commonly found in metabolically abnormal obese when compared to metabolically healthy obese patients [28].

Whole gene expression studies by van Greevenbroek et al. [29] performed in SAT obtained from subjects with familial dyslipidemia showed higher expression of genes of the complement system and genes that regulate such system. The activation of the complement system by local cues in adipose tissue could facilitate the recruitment of immune cells and induce inflammation and insulin resistance in the adipose tissue. Involvement of the complement system in immune cells recruitment is supported by studies with C3a-receptor knockout mice which are protected from high-fat diet insulin resistance and decreased macrophage infiltration.

Studies performed in adipose tissue from subject with insulin resistance have identified the increase in the expression of *SELS*. This correlated with expression levels of cytokines in the adipose cells. It has been suggested that this protein is a serum amyloid-A protein receptor (which is bound to high-density lipoprotein, HDL) which can trigger the onset of insulin resistance. However, the exact functional relationship of this protein with insulin resistance is still under debate [30, 31]. Another protein regulated during insulin resistance and T2D is GSTA4 which plays a role in the elimination of lipid peroxidation products. Levels of GSTA4 decrease at the onset of insulin resistance and T2D since the primary enzymatic method for lipid aldehyde detoxification is via GSTA4-dependent glutathionylation. In part, it may explain the increase in protein carboxylation, reactive oxygen species (ROS) production, and mitochondrial dysfunction observed in such metabolic diseases [32].

Intake of *n*-3 polyunsaturated fatty acid (PUFA) by mice also downregulates the expression of proinflammatory genes such as caspase 1, *Nlrp3*, and *Il1b*, and it is thought that something similar occurs in humans [33].

Other studies have also reported increase in gene expression of oxidative phosphorylation, ribosome genes, and decrease expression of genes coding proteins participating in the WNT and MAPK signaling pathways in adipose tissue in response to exercise, which is recommended to persons with the risk of developing metabolic alterations and obesity [34].

Another study in patients that underwent two-step bariatric surgery (BS) separated by 12 months indicated an increased expression of cell death-inducing DFFA-like effector A (CIDEA) and LPIN1. Both genes are involved in the formation of lipid droplets in fat depots in response to significant weight loss as well as after treatment with the PPARγ agonist rosiglitazone [35]. Adequate triacylglyceride (TG) deposition in adipose tissue is necessary to prevent fatty acid overload in the skeletal muscle and liver [36]. Another gene associated with TG metabolism whose expression is augmented in adipose tissue of patients that underwent weight loss due to laparoscopic gastric banding surgery is the gene

PNPLA3. This gene negatively correlated with BMI, fasting glucose, and fasting insulin and encodes a triacylglycerol lipase that mediates triacylglycerol hydrolysis in adipocytes and has been associated with nonalcoholic fatty liver disease (NAFLD) [37]. It has been demonstrated that Lpin-1 expression levels in adipose tissue correlate with a favorable metabolic profile and expression of fatty acid oxidation genes [38]. Those two genes correlate positively with whole-body insulin sensitivity [35]. The same study observed that the expression of the genes associated with metabolic reactions involved in NAD+ (NMNAT2) and glutathione (NNT) is significantly increased in adipose tissue depots after surgery-induced weight loss. This can explain the better response toward ROS which is observed after BS [35]. Another distinctive observation was the modulation of expression of genes associated with branched chain amino acid metabolism (*BCAT1* and *BCAT2*). Both genes participate in the catabolism of chain branch amino acids (BCAA) whose levels increase in plasma from obese patients.

In animal models with rats which underwent Roux-en-Y gastric bypass (RYGB), the improvement of metabolic parameters was accompanied by a decrease in the expression of *NLRP3* and other inflammation-related genes (*IL-6*, *MCP-1*, *IL-18*, caspase-1 and apoptosis-associated speck-like protein) in omental fat [39]. This observation straightens the role of inflammation in the downregulation of glucose homeostasis. This coincides with the observations of diabetes remission accompanied with an improvement of inflammation, insulin resistance (IR), and other relevant parameters reported in diabetic patients that underwent the same surgery [40].

Similarities between the gene expression profile of adipose tissue of diabetic patients and obese individuals were found. Decrease in the expression of genes related to oxidative phosphorylation (carbohydrate, amino acid, and lipid metabolism) and an increase in expression of genes involved in inflammation and glycan degradation were found [41]. Among the differentially expressed genes, *ELOVL6*, *GYS2*, *FADS1*, *C12orf39*, *SAA1*, *STOX1*, *CASQ2*, *AGPAT9*, *FADS2*, and *B4GALT6* show a lower expression in diabetic patients, while *SPP1* (*OPN*), *TM4SF19*, *MMP9*, *CCL18*, *PRG4*, *IL1RN*, *PLA2G7*, *MSR1*, *VSIG4*, and *LGI2* show a higher expression in diabetic compared with nondiabetic patients [41]. This same study reported that the most regulated pathways in diabetic patients participate in the amino acid metabolism, carbohydrate metabolism, lipid metabolism, and energy metabolism. Some basal transcription factors are downregulated, while genes in the glycan biosynthesis, immune system, and signaling molecules pathways were upregulated [41]. These results in regulated gene expression are very similar to the regulation described with diet, BMI, IR, exercise, and bariatric surgery. This shows the strong relationship between T2D, bad dietary, and exercise habits.

Pancreas

The pancreas is an endocrine gland which has important roles in glucose homeostasis. It has the capacity to produce hormones such as insulin, glucagon, somatostatin, and pancreatic polypeptide but also secrete other enzymes involved in digestion. This gland contains specialized cells such as β-cells, α-cells and γ-cells, PP-cells, and epsilon cells; each can secrete certain hormones. Failure in the functions of this gland leads to the development of type 1 and 2 diabetes. T1D is characterized by a complete ablation of insulin secretion, while T2D is characterized by partial impairment of insulin secretion and insulin resistance that worsens with time. In this chapter, we will discuss gene expression changes that occur in the human pancreas when T2D develops.

Although the pancreas is a highly specialized organ, one study indicates that only 0.7% of all the genes coded in the genome are enriched in the pancreas. This represents approximately 146 genes, but its expression accounts for up to 68% of all the mRNA found in the pancreas. Significant quantities of these expressed genes are secreted proteins involved in the digestive metabolism. Forty-three additional genes mainly associated with neuroendocrine functions were enriched specifically in Langerhans islets [42]. Some of the genes that have the most elevated mRNA expression are shown in the Table 11.1.

The same study found that gene expression in β-cells is responsive to inflammatory cytokines. When exposed to pro-inflammatory molecules, 20% of the transcripts showed modification in their expression levels [42]. Many of these regulated transcripts were related to apoptosis and inflammation. This is highly relevant since diabetes is characterized by the development of low-grade chronic inflammation which promotes a pro-inflammatory environment in several tissues. Inflammation is accompanied by a decrease in the production of insulin which may precede β-cell death. This is in agreement with observations that T2D patients have a reduced β-cell mass, partially due to an increased apoptosis rate which is the results of factors such as gluco- and lipotoxicity and the increase in inflammatory cytokines. It has been reported that during the evolution of T2D, the pancreatic stone protein/regenerating protein (PSP/reg) is upregulated in β-cells and its levels correlated with the duration of diabetes. This protein is related to islet cell regeneration and diabetogenesis [43]. Another gene whose product participates in the regulation of β-cell apoptosis is *MST1* which under diabetologic conditions is transcribed and translated. Its activation leads to the ubiquitination of the important transcription factor PDX1 and induce the mitochondrial-dependent pathway of apoptosis. Downregulation of *PDX1* has an impact in the expression of insulin and *GLUT2* [44]. The potential of the transcription factor Pdx1 to induce the differentiation of acinar cells into β-cells was tested by creating transgenic

Table 11.1 Genes whose expression is elevated in islets of Langerhans (adapted from [42])

Gene	Description	Function
INS	Insulin	Lowering blood glucose
GCG	Glucagon	Elevating blood glucose
SST	Somatostatin	Regulation of endocrine system
PPY	Pancreatic polypeptide	Regulation of pancreatic and gastrointestinal functions
NKX6-1	NK6 homeobox 1	Transcription regulation in β-cells
PAX6	Paired box 6	Development and differentiation of α-cells
NPTX2	Neuronal pentraxin II	Excitatory synapse formation
SCG5	Secretogranin V (7B2 protein)	Regulation of secretory pathways
SCGN	Secretagogin, EF-hand calcium binding protein	Calcium influx and cell proliferation
GAD2	Glutamate decarboxylase 2 (pancreatic islets and brain, 65 kDa)	Autoantigen in diabetes
PTPRN	Protein tyrosine phosphatase, receptor type, N	Autoantigen in diabetes
IAPP	Islet amyloid polypeptide	Inhibition of insulin-stimulated glucose utilization and glycogen deposition
CFC1	Cripto, FRL-1, cryptic family 1	Embryonic development
FAM159B	Family with sequence similarity 159, member B	Unknown
RBPJL	Recombination signal binding protein for immunoglobulin kappa J region-like	Putative transcription factor
RGS9	Regulator of G-protein signaling 9	Regulation of dopamine/opioid signaling

mouse where *Pdx1* expression was inducible. The result was the generation of endocrine precursor cells which migrate into the pancreatic islets and differentiate into insulin-, somatostatin-, and PP (pancreatic polypeptide)-producing endocrine cells [45]. Thus, deregulation of this transcription factor results in hyperglycemia worsening [46].

In the β-cell fractions from diabetic patients, the expression of *UCHL1* (an important component of the deubiquitin system) is lower than in cells from nondiabetic individuals. This results in endoplasmic reticulum stress duo to an additional reduction in proteasomal activity. Higher expression of the endoplasmic reticulum stress proteins *BIP*, *CHOP*, and *GADD34* was found in β-cell fractions from T2D patients. It is in agreement with the observed reduction in β-cell function and survival described in diabetic patients [47]. Inflammatory cytokines produced during the development of T2D are other source of damage to the pancreas. It has been demonstrated that treatment of nondiabetic human islets with palmitate (saturated fatty acid associated with cardiovascular risk) results in the development of an inflammatory response characteristic of T2D patients. This comprise the induction of chemokines and cytokines such as IL-1β, TNF-α, IL-6, IL-8, chemokine (C-X-C motif) ligand 1 (CXCL1), and chemokine (C-C motif) ligand 2 (CCL2). It is proposed that the palmitate-induced NF-kB activation and the signaling through IL-1β is key to the inflammatory process [48]. In addition, some data indicate that during fatty acid-induced β-cell apoptosis, NF-kB activation is responsible for the downregulation of *PGC-1α* expression which acts as a transcriptional coactivator in the regulation of energy metabolism genes [49].

One feature of T2D is an abnormal lipid profile. Particularly, lipotoxicity due to exposure to saturated fatty acids is a predictor of the development of insulin resistance and T2D. Chronic exposure to palmitate, the most common saturated fatty acid impairs β-cell function in part by inhibition of the expression of the insulin gene [50]. However, this is not the only gene whose expression is altered due to continuous exposure. Pathway analysis showed upregulation of genes belonging to functions such as cell death, cellular movement (mainly chemokines), cellular development, gene expression, and lipid metabolism, while downregulated genes correspond to categories of cellular movement, cell morphology, lipid metabolism, molecular transport, and small molecule biochemistry. Palmitate inhibited expression of important transcription factors in β-cells such as *PDX1*, *PAX4*, *PAX6*, *FOXA2*, *MAFA*, *MAFB*, and *NEUROD1* [51]. PDX1 and PAX4 have important roles in developing and maintaining pancreatic islet function [44, 52], and SNPs in these genes have been associated with maturity onset diabetes of the young (MODY) [53]. Mutations in *PAX6* cause abnormal glucose metabolism by deregulating the proinsulin processing via modulation of *PC1/3* production which is a protein-cleaving enzyme [54]. *FOXA2* and *FOXA1* are major regulators of glucose homeostasis, the first by controlling the expression of glucagon, *MAFB*, and the ATP-sensitive channel KIR6.2 which controls insulin secretion in β-cells [55]. Other observations indicate that alleviation of hyperglycemia in mouse models is beneficial for the expression of the transcription factors *Pdx1* and *Mafa* and their targets insulin 1, glucose transported (*Slc2a2*), and Glp-1 receptor (*Glp1r*) in islets [56].

Palmitate inhibited the expression of other genes associated with T2D (*ASB9*, *GLRA1*, *MIA2*, *PRSS35*, *RAB15*, *RASGRP1*, *SEMA6D*, *TBC1D4*, *TSPAN4*, *TSPAN8*, *KCNK16*, *ADCY5*, *ADRA2A*, *TP53INP1*, *CDC123*, *PRC1*, *TCF7L2*, *GLIS3*, *HNF1B*, and *SLC30A8*). On the contrary, palmitate upregulated the expression of *LOC388022*, *C2CD4A*, *ADAMTS9*, and *SPRY2* [51, 57–59]. Islets exposed to palmitate also showed a reduction of proteasome activity,

lower stimulated insulin secretion, and higher caspase activity [47, 58]. To counteract the negative impact of lipotoxicity in β-cell survival, the cells have evolved a mechanism in which the enzyme prohormone convertase 1/3 (*PC1/3*) is upregulated. This enzyme is key in the processing of proglucagon into GLP-1 peptides in α-cells which is able to enhance cell survival through its interaction with its receptor GLP-1R [60, 61].

Hall and Volkov [58] found that a short exposure of islets to palmitate have an impact in the expression of genes in the glycolysis/gluconeogenesis, pyruvate metabolism, and biosynthesis of unsaturated fatty acid pathways. Downregulation of several genes that are part of the respiratory chain was described too. This may have a negative impact in ATP production and insulin secretion [58]. Palmitate also has an impact on the overall methylation of DNA which has been demonstrated to have a strong correlation with gene expression [58]. In fact, studies comparing DNA methylation between diabetic and nondiabetic T2D donors have identified candidate genes that influence insulin secretion which is a hallmark of T2D. Hypermethylation of CpG sites was found in 853 genes. Some of those demonstrated T2D susceptibility genes such as *TCF7L2*, *FTO*, and *KCNQ1*. From the differentially methylated genes, *CDKN1A*, *PDE7B*, *SEPT9*, and *EXOC3L2* also showed differential expression in islets from T2D and nondiabetic donors. Overall, the study found that many of the hypermethylated regions that showed difference between T2D and nondiabetic donors are located in the intergenic regions, around the transcription start site (TSS) and the 3′UTR region. It is worth to notice that several of the SNPs associated with T2D that have been found in GWAS are located in intergenic regions where silencers or enhancers are regularly placed. This may be an indication of a link between these variants, methylation of DNA, and gene expression [62].

Alterations in epigenetic regulation influence insulin secretion as well. Previous studies have shown that epigenetic regulation in islets from T2D patients lead to a lower expression of *PPARGC1A* which results in decreased insulin secretion [63]. Other genes that have been associated with a decrease in insulin secretion are *CHL1*, *LRFN2*, *RASGRP1*, *PPM1K*, *TSPAN33*, *NT5E*, *TMED6*, and *PAK7* [64].

T2D is characterized by an increase in glycosylated hemoglobin (HbA1c) which is an indicator of historic glucose levels in the patients. Thus, HbA1c values are a good indicator of noncontrolled T2D and indirectly could be related to pancreatic function. To date, variants associated with HbA1c explain only a small portion of the increase in HbA1c, but gene expression analysis comparing islets from diabetic and nondiabetic patients has identified ten genes which can explain 24% of the variance in HbA1c. These genes are *JAZF1*, *CHL1*, *LRNF2*, *RASGRP1*, *ABCC8*, *RASGRF1*, *KLHDC5*, *ELAVL4*, *KCNJ11*, and *SLC2A2* [51]. This is highly significant since a detailed study of the function of these few genes may render clues on the pathophysiology of T2D.

No protein-coding genes have been implicated in pancreatic damage as well. Multiple studies have demonstrated that long noncoding RNAs (lncRNAs) have a role in gene regulation, mainly by controlling the transcription of protein-coding genes in *cis*. These transcripts are synthetized by the cell, but they do not contain any protein coding sequence. When ill-regulated, they are associated with pathogenic roles. Particularly, it has been shown that expression of the lncRNA *KCNQ1OT1* is increased, while *HI-LNC45* is decreased in T2D islets. *HI-LNC45* regulates the expression of the transcription factor *GLIS3* which contains variants in the gene body that are associated with T2D. *GLIS3* is mutated in a form of monogenic diabetes as well [65]. *GLIS3* can regulate the expression of *MAFA*, *INS2*, and *GLUT2* and inhibit glucose oxidation and insulin secretion and is involved in the development of β-cells and modulates pancreatic β-cell apoptosis [66]. On the other hand, *KCNQ1OT1* is involved in the silencing of the *KCNQ1* gene which has variants associated with T2D, gestational diabetes, and glucose levels [67–69]. The conserved long noncoding RNA *βlinc1* is able to regulate hormones such as insulin and somatostatin as well as a number of nearby islet-specific transcription factors needed for the proper development and function of Langerhans islets [70]. Although lncRNAs are regulators of other genes, it has been demonstrated that some lncRNA genes are subjected to epigenetic modifications and transcriptional regulation as well [71]. microRNAs (miRNAs) have also been associated with transcriptional regulation of several genes in the pancreas. This double layer of gene regulation may reflect the importance of such genes in functions and processes such as insulin production and secretion, differentiation and proliferation, apoptosis, and survival.

Skeletal Muscle

The skeletal muscle is considered the major site of glucose uptake in the organism, approximately 75% of glucose uptake after a meal occurs, and is metabolized in the skeletal muscle where insulin plays a key role. In normal conditions, insulin binds to the insulin receptor (IR) which is self-phosphorylated and activates the signaling pathway which results in the translocation of the glucose transporter 4 (GLUT4) to the membrane. The presence of GLUT4 in the membrane is required to transport glucose into the cells of the organs with sensitivity to insulin such as the skeletal muscle and the adipose tissue. However, T2D is characterized by a insulin resistance which is characterized by the loss of the insulin capacity to trigger the glucose uptake into the cells, despite of normal or high serum insulin concentrations.

Multiple pathways have been described to contribute to the pathogenesis of insulin resistance: alterations in the insulin signaling, mitochondrial oxidative metabolism and ATP production, fatty acid oxidation, proinflammatory signaling, and modifications in β-cell development and metabolism.

It is known that T2D is a multigenic disease and involves changes in the expression of several genes in different biological pathways. For this reason, the transcriptomic analysis has been useful to identify gene expression profiles on specific tissues that are related to the pathogenesis of this disease and predict possible complications or provide new therapeutic targets for the treatment of T2D. However, due to the large list of genes that reportedly change their expression in T2D and that the gene expression can vary depending of several factors such as diabetes model, ethnicity, age, gender, pharmacological treatment, stage of diabetes, etc., it is difficult to interpret the results obtained by transcriptomic studies. In Table 11.2, we summarized the most commonly expressed genes in skeletal muscle, arranged by metabolic pathway, from studies with diabetic patients or murine models of diabetes [72–77].

Carbohydrate Metabolism

Most of the studies in gene expression of skeletal muscle have found an impaired expression of important genes involved in the transport of glucose, insulin pathway, and metabolism of glucose, for example, insulin receptor substrate-1 (*IRS1*), glycogen synthase (*GYS1*), uncoupling protein 3 (*UCP-3*), GLUT4 (*SLC2A4*), hexokinase II (*HK2*), phosphatidylinositol 3-kinase (*PI3K*), mitogen-activated protein kinase (*MAPK*), and serine-threonine kinase (*AKT*). Although several of these genes have showed changes in their expression in T2D in previous studies, none of them has emerged as a leading candidate responsible for diabetes. Several authors have proposed that the study of the coordinated pattern of gene expression could be more useful to identify the mechanisms involved in the pathogenesis of the disease and to propose potential new targets for the therapy of diabetes.

Lipid Metabolism

The metabolism in skeletal muscle in T2D involves an increased demand of fatty acid oxidation for its energy needs when glucose is not available. This alteration in lipid metabolism has been related to the accumulation of lipids in the skeletal muscle, a key mechanism involved in insulin resistance development. The expression profiles observed in different studies on skeletal muscle samples from human or murine models of diabetes were controversial; some of them agree with a significant increase in the mRNA for proteins involved in the fatty acid oxidation pathways, whereas some others described a significant decrease on the same genes. Similar discrepancies were found on the expression of β-oxidation pathway genes.

An altered lipid metabolism is also present in obesity, which has been considerate one of the main factor related to insulin resistance and T2D development. In this regard, the fat mass and obesity-associated gen (*FTO*) (a well-characterized gen associated with the increase in obesity risk) is expressed in tissues related to metabolic diseases, including skeletal muscle and adipose tissue. However, there are many inconsistences when the *FTO* expression in adipose tissue is related to obesity. On the other hand, some gene polymorphisms in the *FTO* gen have been associated with T2D in several populations, and their expression was related to defects in glucose and lipid metabolism in skeletal muscle and adipose tissue. In a study where the *FTO* expression in skeletal muscle from obese nondiabetic subjects was compared with type 1 and T2D patients, it was found that in T2D patients, *FTO* increases their expression at mRNA and protein levels, whereas the expression in obese nondiabetic subjects and T1D patients was unchanged. To probe the specific actions of *FTO* expression, it was overexpressed in myotubes, resulting in decrease expression of oxidative phosphorylation and antioxidant genes, increased lipid accumulation, and increased oxidative stress, similar to what was observed in the diabetic skeletal muscle, suggesting that FTO may contribute to the muscle alterations observed in T2D. Interestingly, *PGC-1α* gene was downregulated in diabetic patients, as was reported previously, but *FTO* overexpression did not modify the expression of *PGC-1α* in human myotubes [78].

Mitochondrial Function

It is important to note that despite the differences in experimental methods and ethnicity in the analyzed subjects from several studies, they agree that there is a significant decrease in the expression of genes involved in mitochondrial function. These studies in muscle biopsies from diabetic patients have reported a decrease of multiple components of the mitochondrial respiratory chain, and mainly, the oxidative phosphorylation (OXPHOS) pathway. Mitochondrial OXPHOS is an important source of reactive oxygen species (ROS), such as superoxide anions, hydrogen peroxide, and hydroxyl radicals that are formed by products of cellular metabolism. The ROS have been implicated in the development of insulin resistance. Interestingly, patients without T2D but with a family history of diabetes have a decrease expression in genes of OXPHOS pathway, suggesting that alterations in gene expression of this pathway could be related to the initial steps for T2D development [77].

Table 11.2 Summary of genes with altered expression in skeletal muscle samples from diabetic patients or animal models of diabetes

Gene	Description	Function	Expression
Carbohydrate metabolism			
SLC2A4	Solute carrier family 2 member 4 (GLUT4)	Glucose transport into the cells	↓
INSR	Insulin receptor	Insulin pathway	↓
AKT1	Serine/threonine kinase	Insulin pathway	↓
IRS-1/2	Insulin receptor substrate 1/2	Insulin pathway	↓
PIK3	Phosphatidylinositol 3-kinase	Insulin pathway	↓
GYS1	Muscle glycogen synthase	Glucose storage	↓
PTPN11	Protein tyrosine phosphatase, non-R type 11	Insulin pathway	↓
MAPK 4, *8*, *12*	Mitogen activated protein kinases	Insulin pathway	↓
PKC-ζ	Protein kinase C (PKC)-ζ	GLUT4 translocation	↓
HK2	Hexokinase II	Phosphorylates the glucose after uptake by the cell	↓
FBP2	Fructose-1,6 biphosphatase 2	Glucose metabolism	↑↓
Lipid metabolism			
FABP1	Fatty acid transporter type 1	Regulates the uptake of long chain fatty acids to muscle cells	↑
LIPE	Hormone-sensitive lipase	Contributes to increase the pool of nonsterified fatty acids in the cytosol	↑↓
LPL	Lipoprotein lipase	Hydrolyses triglycerides	↑↓
MGLL	Monoglyceride lipase	A key enzyme in triglyceride hydrolysis	↑↓
ACADM	Acetyl-CoA dehydrogenase	It is a rate-limiting enzyme catalyzing the first dehydrogenation of fatty acids	↑
ETFB	Electron transfer flavoprotein-β	It is an electron acceptor protein for many dehydrogenases in the mitochondria	↑
ECI	Δ^3, Δ^2-enoyl-CoA isomerase	Required for β-oxidation of unsaturated fatty acids	↑↓
SCD	Steroyl-CoA desaturase	A rate-limiting enzyme in unsaturated fatty acid synthesis	↓
LOC51706	Cytochrome b_5 dehydrogenase	A rate-limiting enzyme in unsaturated fatty acid synthesis	↓
OXCT1	Succinyl-CoA: 3-oxoacid-CoA transferase	A rate-limiting first step in extra hepatic metabolism of ketone bodies	↓
PPARα	Peroxisome proliferator-activated receptor α	Lipid metabolism	↓
Mitochondrial function			
PKM	Pyruvate kinase	Protein involved in glycolysis	↓
PDHA	Pyruvate dehydrogenase	Catalyzes conversion of pyruvate to acetyl-CoA and CO_2	↓
ATP5B	ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide	Synthesis of ATP	↓
SLC25A4	Solute carrier family 25 member 4	Involved in ADP/ATP flux between cytosol and mitochondria	↓
PGC1α	PPARγ coactivator 1α	Transcriptional coactivator that regulates genes involved in energy metabolism	↓
PGC1β	PPARγ coactivator 1β	Transcriptional coactivator that regulates genes involved in energy metabolism	↑↓
UCP3	Uncoupled protein 3	Mitochondrial protein expressed mainly in the skeletal muscle, participate in the fatty acid metabolism	↓
SOD2	Superoxide dismutase 2	Mitochondrial protein with antioxidant properties	↓
NDUFB2	NADH dehydrogenase-ubiquinone 1 beta subcomplex, 2	Electron transport chain	↓
NDUFB5	NADH dehydrogenase-ubiquinone 1 beta subcomplex, 5	Electron transport chain	↓
NDUFC2	NADH dehydrogenase-ubiquinone 1, subcomplex, 2	Electron transport chain	↓
SDHB.	Succinate dehydrogenase cytochrome b subunit	Electron transport chain	↓
NNT	Nicotinamide nucleotide transhydrogenase	NADPH production and involved in the antioxidant system	↓
UQCRC2	Ubiquinol cytochrome c reductase core protein II	Electron transport chain	↓
HSP70	Heat shock protein 70	Involved in protein folding process	↑↓
NRF-1	Nuclear respiratory factor 1	Transcription factor	↓

The arrows represent up (↑) or down (↓) regulated genes [72–77]

Most of the genes involved in OXPHOS pathway are encoded in the nuclear genome, and their expression is regulated by transcription factors. Particularly, the expression of the nuclear respiratory factor-1 (NRF-1) has demonstrated a key role in diabetes. In the skeletal muscle from diabetic patients, the expression of the nuclear respiratory factor-1 (NRF-1) was decreased as well as genes regulated by the NRF transcription factor family. The promoter region from several OXPHOS genes has been reported to contain binding sites for NRF-1, suggesting that this gene contributes to the diabetes-related expression pattern in diabetes. In this regard, NRF-1 has been proposed as an important gene that modulates mitochondrial biogenesis, respiratory capacity, and the glucose transporter protein GLUT4 [77].

In addition, the peroxisome proliferator-activated receptor (PPAR) gamma coactivator-1 (*PGC-1α*) gene has been proposed as a master regulator of mitochondrial gene expression that mediates the oxidative phosphorylation expression phenotype in prediabetic and diabetic patients. The PGC-1α is a transcriptional regulator that does not bind directly to the DNA but influence transcription by interacting with other transcription factors, modifying the chromatin or altering protein-protein interactions within the transcriptional complex. In diabetes, PGC-1 not only activates NRF but also PPARα, PPARγ, hepatocyte nuclear factor 4, and other transcriptions factors critical for the metabolic function [77, 79]. Interesting, members of the PGC-1 family, PGC-1α and PGC-1β, had a significant reduction on their expression that correlates with a decrease in OXPHOS gene expression in patients with T2D [80]. On the contrary, when the PGC-1α was overexpressed in a muscle cell line, an upregulation of OXPHOS genes was observed in a time-dependent manner [79].

The Role of Insulin in Gene Expression

The changes in glucose metabolism observed in T2D are related to insulin resistance, which has been proposed as one of the initial steps related to T2D development. Insulin is a hormone released by the pancreas, specifically by β-cells, which has an extensive capability to regulate gene expression. Some published investigations indicate that the insulin action in skeletal muscle may modify the expression of around 800 genes related to signal transduction, vesicular traffic, and cytoskeletal function and fuel metabolic pathways [81, 82]. These effects have been related with changes on at least 70 transcription factors involved in the insulin response. Some of them that stand out are *RRAD*, *IGFBP5*, *INSIG1*, and NGF1-B (*NR4A1*), which were upregulated in L6 skeletal muscle cells [82].

As was mention before, the action of insulin on gene expression is very important to regulate genes on specific metabolic pathways. To determine the direct contribution of insulin on the altered expression in T2D, the group of Yechoor et al. analyzed the gene expression profiles on a muscle insulin receptor knockout mice (MIRKO) and compared it to controls (Lox-controls) under three different conditions: (1) at basal state, (2) after streptozotocin (STZ)-induced diabetes, and (3) after STZ-induced diabetes rendered euglycemic with insulin treatment. The results obtained demonstrated that insulin action has a role in maintaining basal expression levels in 1% of the genes in comparison to 4% of genes that are altered in diabetes. Although insulin is not associated with these changes at basal state, it was observed that insulin receptor is required to reverse the effects induced by diabetes. Suggesting that the presence of an intact insulin-signaling system is needed to return its expression toward normal [76]. This phenomenon was also observed in humans where at early stages of T2D, high serum insulin levels are commonly observed and were related to an increase in the expression of insulin pathway genes, possibly as a mechanism to compensate elevated serum levels of glucose. However, this compensatory effect is lost in people with T2D where the expression of insulin signaling molecules is reduced [73].

Liver

The liver is an important organ that participates in the homeostasis and metabolism of glucose. Hepatic glucose metabolism includes glucose transport, glycolysis, gluconeogenesis, glycogen synthesis, and glycogenolysis. In fed state, the liver synthesizes and stores glycogen in response to insulin stimulation, whereas in fasting state, the liver activates the gluconeogenesis and releases glucose in response to glucagon stimulation. An imbalance in the metabolism of hepatic glucose has been related to the T2D development, where hyperglycemia correlates with hepatic insulin resistance.

The hepatic glucose homeostasis is maintained by many enzymes involved in hepatic glucose metabolism that have been proposed as potential targets in diabetes, for example, glucokinase (*GCK*) the key enzyme of glycolysis; fructose-1,6-biphosphatase (*FBP1*); phosphoenolpyruvate carboxykinase (*PCK1* and *PKC2*); and glucose 6-phosphatase (*G6PC*) control key points in the gluconeogenesis pathway. Glycogen phosphorylase (*PYGL*) is a rate-limiting enzyme of glycogenolysis [83]. G6PC and GCK act in opposition to regulate the intracellular levels of free glucose. An increased ratio of G6PC/GCK promotes a glucose efflux to the bloodstream, whereas a decreased ratio causes glucose influx. The GCK activity has been reported to decrease in patients with T2D. A decrease of 60% in *GCK* expression has been observed in diabetic subjects with HbA1c >7.0 that also correlates nega-

tively with Hb1Ac and fasting glucose, suggesting an important dysregulation of hepatic *GCK* expression in diabetes [84]. On the other hand, in fasting conditions, normoglycemia is maintained by hepatic gluconeogenesis, controlled by rate-limiting enzymes such as *FBP1*, *PCK1*, and *G6PC* that are regulated by insulin. An alteration in gluconeogenesis is observed in T2D. It has been related to an increased expression of *FBP1*, *PCK1*, and *G6PC* due to the incapacity of insulin to suppress their expression due to hepatic insulin resistance.

It has been described that transcriptional activation of *PCK* requires the coactivation of the glucocorticoid receptors and the liver-enriched transcription factor hepatic nuclear factor-4α (*HNF4A*) by *PGC-1α* [85]. The *PGC-1α*, as mentioned before, is a key regulator of the OXPHOS-related genes in other tissues such as skeletal muscle, producing a downregulation of the OXPHOS pathway in DT2. On the contrary, several genes in the OXPHOS pathway appear to be upregulated in the liver from diabetic patients (Table 11.3). However, no correlation was observed between the expression of *PGC-1α* and the upregulation of genes involved in OXPHOS in the liver of patients with T2D [86].

Like OXPHOS pathway, other metabolic pathways have been shown to differ in their expression pattern when compared with other insulin-sensitive tissues. For example, several genes co-expressed in the liver, skeletal muscle, and adipose tissue, related to glycolysis/gluconeogenesis, fatty acid beta oxidation, tricarboxylic acid cycle, and electron transport chain pathways, are downregulated in skeletal muscle and in adipose tissue but are upregulated in the liver from diabetic patients [75].

The lipid metabolism is well known to be altered in the diabetic liver. Interestingly, none of the expression enzymes related to fatty acid metabolism, including fatty acid oxidation, fatty acid synthesis, and fatty acid storage were downregulated in the liver of diabetic mice. On the contrary, enzyme genes involved in fatty acid oxidation (*CPT1a*, *CPT2*, *EHHADH*, ACOT2, *ACOT3*, *ACOT4*, *ACOT5*, *ACOT6*, and *PPARα*) and fatty acid storage (*ELOVL6*, *SCD1*, *GPAT*, *DGAT1*, and *DGAT2*) were significantly upregulated, whereas the genes involved in fatty acid synthesis (*ACLY* and *FASN*) showed no significant changes. In addition, genes related to fatty acid transport (*CD36* and *SLC27a2*) were also upregulated in the liver of diabetic mice, showing that enhanced fatty acid transport is consistent with the increased expression of enzyme genes related to fatty acid storage. These data suggest that diabetes enhances liver fatty acid oxidation, which has been reported to stimulate gluconeogenesis and suppress glycolysis. In this sense, it was reported that key enzymes in glycolysis such as pyruvate kinase, phosphofructokinase, and glucokinase enzyme activity and mRNA expression are decreased in diabetes. However, in the liver of diabetic mice, no changes in pyruvate kinase or phosphofructokinase expression were observed. On the contrary, the *PKLR* gene that encodes the rate-limiting enzymes pyruvate kinase was significantly upregulated, suggesting an increased glycolysis activity in the liver. But this enhanced glucose consumption is not sufficient to decrease the hepatic glucose levels because gluconeogenesis and glycogenolysis were also enhanced to produce more glucose [83].

On the other hand, the inflammation is one important factor that leads to diabetes. Surprisingly the downregulated genes found in diabetic mice liver were mainly enriched in immune-related process, such as adaptive immune response and lymphocyte mediate immunity. However, the results showed that besides inflammatory signaling, another hepatic immune-related pathway is also correlated to T2D. For example, the downregulated genes in diabetic mouse liver were also enriched in pathways related to cancer, hepatitis, adenovirus infection, and liver tumor. These data are consistent with previously reported data that reported an increase in the frequency of hepatitis B and C virus infection in diabetic patients. That is in line with the association of hepatitis with T2D. Furthermore, epidemiological studies have reported that liver cancer is increased in diabetic patients; however the biological mechanism is still unknown [83].

Table 11.3 OXPHOS genes upregulated in patients with T2D [86]

Gene	Description	Function
NDUFA6	NADH: ubiquinone oxidoreductase subunit A6	Electron transport chain
SDHC	Succinate dehydrogenase complex subunit C	Electron transport chain
UQCRB	Ubiquinol-cytochrome c reductase-binding protein	Electron transport chain
COX4i1	Cytochrome c oxidase subunit 4i1	Electron transport chain
ATP5B	ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide	ATP synthesis

Whole-Blood Gene Expression in DT2

Studies of gene expression in peripheral blood mononuclear cells (PBMCs) have identified changes in more than 1000 genes which are differentially expressed in diabetic patients. Those genes were grouped according to their function, and changes in profile expression of several signaling pathways were observed when compared with subjects without diabetes.

The most important pathways altered in T2D patients were OXPHOS, MAPK, electron transport chain pathways, fatty acid metabolism, inflammatory response, and DNA repair [85, 87]. However, some of the altered genes were involved in two or more biological process, such as *RELA*, *UCP3*, *STAT5B*, *PLD2*, *PSEN2*, *IL17A*, and *CRCP* (upregulated

Table 11.4 Genes expressed in the WBC, adipose tissue, liver, and skeletal muscle related to the progress of T2D

Gene	Description	Function
FABP5	Fatty acid binding protein 5	Protein involved in the fatty acid uptake, transport, and metabolism has been associated with the development of insulin resistance and T2D in obesity
CFD	Complement factor D	Serine peptidase protein secreted by adipocytes that has been implicated with insulin secretion in mice
PC-1	Ectonucleotide pyrophosphatase/phosphodiesterase 1	Transmembrane protein that acts as an inhibitor of the insulin pathway and has been related to insulin resistance
UCP3	Uncoupling protein 3	Mitochondrial protein expressed mainly in skeletal muscle, it participates in the fatty acid metabolism and has been observed a decrease in their expression in patients with T2D

genes involved in inflammation, response to hypoxia and oxidative stress, and fatty acid response), as well as *ARNT*, *CAT*, and *MDH2* (downregulated genes implicated in response to oxidative stress, DNA repair, and response to hypoxia) [87]. Interestingly, the pathways involved in stress response, such as MAPK, TNF signaling, apoptosis, and mTOR signaling, were significantly altered after glycemic control [85].

The ceramide and adipocytokine signaling pathways were significantly upregulated in T2D patients, probably as a result of the presence of obesity in the patients. In the case of ceramides, they are lipids related to structural components of the cell membrane. However, an increase of ceramide production has been associated with different stress stimuli such as inflammatory mediators, heat, UV radiation, hypoxia, chemotherapeutics, and oxidative stress. High levels of ceramides are involved in the inhibition of AKT/PKB, resulting in insulin resistance. It suggests an important link between obesity and diabetes. In addition, the adipose tissue releases several factors including FFA and proteins called adipocytokines (TNF-α, IL-6, and resistin) that control various metabolic functions. Those adipocytokines and the proinflammatory cytokines secreted by the macrophages residing in adipose tissue have been related to insulin resistance development. This phenomenon occurs by the activation of JNK and NF-κB pathways that impair the insulin action by interfering with the insulin binding to its receptor [87]. In this sense, genes related to the JNK pathway were coordinately upregulated in diabetes; however, after glycemic control, a downregulation in this pathway was observed. The gene expression of JNK genes was also significantly correlated to fasting glucose levels and HbA1c. It suggests that the upregulation of the JNK genes in the PBMCs may be associated with hyperglycemia. In this regard, diabetes and hyperglycemia have been related to oxidative stress which causes activation of the JNK pathway by endoplasmic reticulum stress in pancreatic β-cells and hepatocytes. Besides, JNK activation suppresses insulin biosynthesis and impairs insulin action.

On the other hand, the OXPHOS pathway was significantly downregulated in diabetes. However, it was not altered by glycemic control. The altered expression in OXPHOS pathway was correlated with neither fasting glucose nor HbA1c. It suggests that OXPHOS may predict the existence of diabetes, because it was coordinately downregulated in PBMCs of patients with T2D but was not altered by glycemic control. These data are in agreement with the profile expression observed in the skeletal muscle and adipose tissue, where the OXPHOS is one of the main pathways that suffer alteration in gene expression in diabetes [85].

To compare if the gene expression observed in WBC was related to the gene expression in insulin-sensitive tissues such as the liver, adipose tissue, and skeletal muscle, a microarray analysis was performed in OLETF rats. The results showed that more than 300 genes were differentially expressed in blood cells, and only 4 genes were related to the insulin-signaling pathway: *Pc-1*, *Sihps-1*, and *Grb2* were upregulated, and *Pten* was downregulated. In addition, 57 genes were concurrently expressed in the analyzed tissues with the adipose tissue showing the best correlation with WBC, sharing 41 genes. It was followed by the liver with 25 genes and 14 genes with the skeletal muscle. From these 57 genes, only 4 genes have been well related to the progress of T2D (Table 11.4) [88].

Whole-Blood Gene Expression as a Possible Tool for Early Detection of T2D

The diagnosis of T2D is generally obtained by measuring fasting glucose levels, oral glucose tolerance test (OGTT), or percent of HbA1c. However, these methods do not determine the risk to develop T2D at early stages. The expression profile has been proposed as a very good tool to evaluate the risk to develop T2D. However, lack of samples from specific tissues makes difficult to perform this kind of studies. It is not ethically correct to obtain tissue samples from organs involved in the pathogenesis of the disease from healthy humans only for an early diagnosis. For this reason, recent studies have been focused to determine the expression profile on whole blood cells (WBC), which are very accessible. This is a tissue that may show the oxidative stress caused by high levels of glucose, insulin, free fatty acids, and tissue-derived circulating bioactive mediators.

The studies on WBC have demonstrated that gene expression profile in diabetes is different from other pathologies such as metabolic syndrome or coronary artery disease. Suggesting that gene expression profiles in WBC can be useful to identify the altered pathways involved in the patho-

physiology of T2D and pre-clinical symptoms of T2D. This technology can also be used as a new diagnosis method that could predict the progression of the disease.

miRNAs in Blood Samples

Today it is widely recognized that not all the RNAs are traduced to proteins; there are noncoding RNAs named microRNAs (miRNAs). They are involved in gene regulation of specific target genes. The miRNAs are a class of 19–24 nucleotides of RNA, which mediate post-transcriptional gene silencing by binding to the 3′-UTR or open reading frame (ORF) region of target mRNAs. The involvement of miRNAs has been reported in several biological activities including cell proliferation, cell differentiation, cell migration disease initiation, and disease progression [89]. Increased levels of specific miRNAs have been associated with a variety of diseases including cancer, obesity, diabetes, and cardiovascular disease. In the case of diabetes, several studies have reported that miRNAs play a critical role in glucose homeostasis and T2D pathogenesis, because a vast number of miRNAs are implicated in pancreatic development (miR-124a, miR-15a/b, miR-192, miR-375), insulin secretion (miR-9, miR-124a, miR-375), glucose transport (miR-29a/b), and β-cell dysfunction (miR-124a). In addition to the hyperglycemia, miRNAs also participate in the inflammatory response, vascular endothelial damage, and fibrosis processes that are involved in DT2 complications. There is evidence that demonstrates that T2D complications are associated with miRNAs dysregulation in various target tissues, especially the brain, eyes, nerves, and kidneys. For example, the miR-133 highly expressed in diabetic hearts has been associated with long QT syndrome and cardiac hypertrophy, whereas upregulation of miR-192 has been implicated in diabetic nephropathy [90].

In addition to the expression of miRNAs in tissues, they are expressed in many biological fluids such as saliva, urine, breast milk, and blood where its expression is stable. They are found packed into exosomes or microvesicles and as extracellular miRNAs that are loaded into high-density lipoprotein (HDL) or bound to an argonaute protein (AGO2) outside of the vesicles. These conformations protect the miRNAs from degradation and confers them stability in those fluids. The work published by Wang et al. [91] investigates whether there were differences in the serum miRNA expression profiles between T2D patients with or without diabetic microvascular complications, in comparison with nondiabetic patients. The results showed that serum miRNA expression profiles varied among diabetic patients and the healthy group. From the 754 miRNAs evaluated in the array, 25 miRNAs were upregulated, and 118 were downregulated in the two T2D patient groups compared with the nondiabetic controls. The validation analysis showed that five miRNAs (showed in Table 11.5) were significantly increased in both T2D patients with and without complications relative to healthy controls. Furthermore, those five miRNAs were higher in T2D patients with complications than in those who were free of complications [91].

Table 11.5 Significantly upregulated miRNAs found in T2D patient groups in comparison with nondiabetic group [91]

miRNAs	Diabetic complication
miR-661	Regulation of insulin biogenesis and the SNAIL-triggered epithelial to mesenchymal transition that has been related to microvascular complications
miR-571	Chronic liver disease by their participation in fibrogenic and inflammatory process in the liver
	Contribute to kidney fibrosis that is related to diabetic nephropathy
miR-770-5p	Retinopathy and neurological diseases
miR-892-b	Retinopathy and neurological diseases
miR-1303	Tumor/cell cycle-related miRNAs

Recently, a study in adipose tissue of Dicer KO mice (AdicerKO) demonstrated that miRNAs released to the circulation can regulate gene expression in other tissues. For example, the miR99b produced and released to the circulation by the adipose tissue was responsible in modulating the expression of the fibroblast growth factor 21 (FGF21) gen in adipose tissue, as well as in the liver, muscle, and pancreas. Suggesting that miRNAs secreted by the adipose tissue may act at paracrine and endocrine levels [92]. Interestingly, the Dicer KO mice used in this study showed an alteration in glucose levels and insulin resistance. Thus, the miRNAs released by the adipose tissue may affect the glucose metabolism possibly by their influence in insulin-sensitive tissues.

As a summary, the publications reviewed propose that miRNAs detected in the circulation can be used as potential noninvasive biomarkers for various diseases, including T2D and its complications. However, more studies are necessary to validate this hypothesis.

Concluding Remarks

- Changes in the expression of several genes arising before phenotype changes are observed.
- Insulin resistance and insulin secretion are linked to the modification of gene expression in the pancreas, liver, adipose tissue, muscle, and blood.
- Inflammation, oxidative phosphorylation, carbohydrate and lipid metabolism, and mitochondrial function are distinctive pathways that are deregulated during T2D progression.
- Gene regulation in distant organs can be achieved by secreted hormones and microRNAs

Multiple-Choice Questions

1. Mention two transcription factors that participate in the regulation of adipocyte differentiation.
   (a) **PPARγ and C/EBPα (both molecules coordinately regulate the expression of many hundreds of genes responsible for the establishment of the mature adipocyte phenotype)**
   (b) FOXO1 and HIF1
   (c) PDX1 and PGC-1α
   (d) FOXO1 and PDX1
   (e) HIF1 and PDX1
2. Mention one role the NOD-like receptors have in adipocytes of obese individuals.
   (a) Decrease the expression of inflammation-related genes.
   (b) **Induce adipocyte death by pyrosis. (Activation of caspase-1 leading to membrane breakdown and proinflammatory cytokine processing)**
   (c) Increase lipid uptake.
   (d) Increase adipogenesis.
   (e) Sense blood glucose.
3. How is the expression of inflammation-related genes in obese vs. lean individuals?
   (a) Inflammation-related genes expression is lower in obese than in lean individuals.
   (b) Inflammation-related genes expression is the same in obese than in lean individuals.
   (c) **Inflammation-related genes expression is higher in obese than in lean individuals. (This enhanced expression of inflammatory genes is linked to the development of insulin resistance.)**
   (d) Inflammation-related genes expression is not related to obesity.
   (e) Inflammation-related genes expression is not relevant.
4. What effects does saturated fat consumption exert in the pancreas?
   (a) Increases the expression of transcription factors such as PDX1 and PAX4.
   (b) Positively regulates ATP production in the pancreas.
   (c) **It decreases the expression of insulin and induces apoptosis of β-cells. (Inflammation and saturated fat consumption inhibit the expression of important transcription factors in β-cells)**
   (d) Induce macrophage recruitment
   (e) Trigger mechanism to protect from inflammation-induced damage
5. What are the most distinctive pathways that are deregulated in T2D?
   (a) Inflammation, urea cycle, carbohydrate, lipid metabolism, and mitochondrial function
   (b) Inflammation, oxidative phosphorylation, carbohydrate metabolism, nucleotide metabolism, and mitochondrial function
   (c) Xenobiotics degradation, oxidative phosphorylation, nucleotide metabolism, lipid metabolism, and mitochondrial function
   (d) **Inflammation, oxidative phosphorylation, carbohydrate, lipid metabolism, and mitochondrial function (deregulation of genes in these pathways has been observed in the main tissues associated with T2D)**
   (e) Inflammation, oxidative phosphorylation, urea cycle, lipid metabolism, and polar amino acids
6. Which genes are considerate as two key regulators of the expression of OXPHOS pathway related genes?
   (a) *GLUT4* and *FTO*
   (b) *PGC1α* and *SOD2*
   (c) ***NRF-1* and *PGC-1α* (downregulation of OXPHOS genes in diabetes are associated with low expression of NRF-1 and PGC1α genes)**
   (d) *PGC-1β and IRS*
   (e) *PPARα* and *FASN*
7. How PGC-1α can influence the gene transcription?
   (a) Binding directly to DNA and activate the transcription in target genes
   (b) **Interacting whit other transcription factors such as *PPARα*, *PPARγ,* and *HNF4*. (The *PGC-1α* is a transcriptional regulator that does not bind directly to DNA but influence transcription by interacting with other transcription factors including *NRF-1*, *PPARα*, *PPARγ,* and *HNF4*)**
   (c) Activating directly specific sites of the RNA polymerase II increasing their affinity to DNA
   (d) Inhibiting the union site of the transcription factors in the DNA
   (e) Stabilizing the mRNA and inhibiting its degradation
8. Besides the expression pattern in OXPHOS pathway, what other pathways are downregulated in skeletal muscle and adipose tissue but upregulated in liver in diabetic patients?
   (a) **Fatty acid beta oxidation, tricarboxylic acid cycle, glycolysis/gluconeogenesis, and electron transport**
   (b) Inflammation, urea cycle, carbohydrate, lipid metabolism, and mitochondrial function
   (c) Inflammation, carbohydrate metabolism, nucleotide metabolism, and mitochondrial function
   (d) Xenobiotics degradation, oxidative phosphorylation, nucleotide metabolism, lipid metabolism, and mitochondrial function
   (e) Fatty acid transport, urea cycle, glycogenolysis, insulin transport, and glucose uptake

9. What is the tissue that had the best expression pattern correlation with whole blood cells in diabetes?
   (a) Skeletal muscle
   (b) Pancreas
   (c) Liver
   (d) Brain
   (e) **Adipose tissue (the adipose tissue and WBC share the expression of 41 genes, followed by liver with 25, and the skeletal muscle with 14)**
10. Why miRNAs detection in blood stream would be a potential risk marker in diabetes?
   (a) Because they are small noncoding RNAs that can be detected in blood samples
   (b) Because miRNAs are very stable to degradation in blood samples
   (c) Because miRNAs expression is increased in blood samples from DT2 patients
   (d) **Because some miRNAs detected in the circulation are related to gene regulation in altered pathways in diabetes and diabetes complications**
   (e) Because adipose tissue can release miRNAs to blood stream

Further Reading

Bugliani M, Liechti R, Cheon H, Suleiman M, Marselli L, Kirkpatrick C, et al. Microarray analysis of isolated human islet transcriptome in type 2 diabetes and the role of the ubiquitin-proteasome system in pancreatic beta cell dysfunction. Mol Cell Endocrinol. 2013;367(1–2):1–10.
- This paper highlights the importance of the ubiquitin-proteasome system in beta cell dysfunction in human T2D.

Igoillo-Esteve M, Marselli L, Cunha DA, Ladriere L, Ortis F, Grieco FA, et al. Palmitate induces a pro-inflammatory response in human pancreatic islets that mimics CCL2 expression by beta cells in type 2 diabetes. Diabetologia. 2010;53(7):1395–405.
- This paper highlights the role of saturated fatty acids in inflammation and its effect on beta cell.

Danielsson A, Ponten F, Fagerberg L, Hallstrom BM, Schwenk JM, Uhlen M, et al. The human pancreas proteome defined by transcriptomics and antibody-based profiling. PLoS One. 2014;9(12):e115421.
- They employed genome-wide RNA sequencing to identify genes with elevated expression in pancreas.

Yin Z, Deng T, Peterson LE, Yu R, Lin J, Hamilton DJ, et al. Transcriptome analysis of human adipocytes implicates the NOD-like receptor pathway in obesity-induced adipose inflammation. Mol Cell Endocrinol. 2014;394(1–2):80–7.
- This paper describes the role of NOD-like receptor pathway in adipose inflammation.

Hoggard N, Cruickshank M, Moar KM, Bashir S, Mayer CD. Using gene expression to predict differences in the secretome of human omental vs. subcutaneous adipose tissue. Obesity. 2012;20(6):1158–67.
- This paper get light into the proteins that are secreted by adipose tissue and their putative role as signaling molecules.

Patti ME. Gene expression in humans with diabetes and prediabetes: what have we learned about diabetes pathophysiology? Curr Opin Clin Nutr Metab Care. 2004;7(4):383–90.
- This paper review about gene expression of genes related to diabetes pathogenesis.

Wang M, Wang XC, Zhao L, Zhang Y, Yao LL, Lin Y, et al. Oligonucleotide microarray analysis reveals dysregulation of energy-related metabolism in insulin-sensitive tissues of type 2 diabetes patients. Genet Mol Res. 2014;13(2):4494–504.
- In this paper compare the expression pattern of different insulin sensitive tissues from diabetic patients.

Jenkinson CP, Göring HH, Arya R, Blangero J, Duggirala R, DeFronzo RA. Transcriptomics in type 2 diabetes: bridging the gap between genotype and phenotype. Genom Data. 2016;8:25–36.
- This paper described the importance of the transcriptome to identify genes related to diabetes development.

Hayashi Y, Kajimoto K, Iida S, Sato Y, Mizufune S, Kaji N, et al. DNA microarray analysis of whole blood cells and insulin-sensitive tissues reveals the usefulness of blood RNA profiling as a source of markers for predicting type 2 diabetes. Biol Pharm Bull. 2010;33(6):1033–42.
- In this paper compare the expression pattern of different insulin sensitive tissues with RNA expression in blood samples from diabetic patients.

Wang C, Wan S, Yang T, Niu D, Zhang A, Yang C, et al. Increased serum microRNAs are closely associated with the presence of microvascular complications in type 2 diabetes mellitus. Sci Rep. 2016;6:20032.
- This paper focuses on the importance to study the miRNAs expression in blood circulation related to diabetes and vascular complications.

Glossary

3′-UTR region Untranslated regions (UTRs) at the 3′end of mRNA contain important sequences that are related to the regulation of gene translation. The 3′UTR plays a critical role in the stability of mRNA and in post-transcriptional regulation.

Apoptosis Is a process of programmed cell death that is considerate to be important in several processes including normal cell turnover, development and function of immune system, hormone-dependent atrophy, embryonic development, and chemical-induced cell death. Human conditions such as neurodegenerative diseases, ischemic damage, autoimmune disorders, and may types of cancer are related to inappropriate apoptosis.

Bariatric surgery Is a surgical process employed to reduce weight in obese patients, by restricting the amount of food the stomach can hold, causing malabsorption of nutrients. The most common bariatric surgery procedures are gastric bypass, sleeve gastrectomy, adjustable gastric band, and biliopancreatic diversion with duodenal switch.

Damage-associated molecular patterns (DAMPs) Are cell-derived molecules that can initiate and perpetuate immunity in response to trauma, ischemia, and other setting of tissue damage in the absence of overt pathogenic infection. DAMPs can be found in the nucleus and cytoplasm (HMGB1), cytoplasm alone (S100 proteins), exosomes (HSP), extracellular matrix (hyaluronic acid), and in plasma such as complement (C3a, C4a, and C5a). Examples of nonprotein DAMPs include ATP, uric acid, heparin sulfate, RNA, and DNA. Increased levels of DAMPs are associated with inflammatory diseases such as sepsis, arthritis, atherosclerosis, systemic lupus erythematosus, Crohn's disease, and cancer.

Deacetylation Histones acetylation has been linked to transcriptional activation. The enzymes regulating the histone acetylation are the histone acetyltransferases (HATs). On the contrary, the deacetylation by histone deacetylases (HDACs) is related to transcriptional repression.

DNA hypermethylation DNA methylation is a heritable epigenetic mark that involves the covalent transfer of a methyl group to a cytosine ring of DNA. The methylation reaction is catalyzed by a family of DNA methyltransferases (DNMTs). DNA methylation is associated with decreased transcriptional activity.

Enhancer Is a DNA sequence that activators or transcriptional factors bind and increase gene transcription. Its location is variable in the gene; it can be present in the 5′-UTR, in the 3′-UTR, or into the codify region of the gene.

Epigenetics Epigenetics is the study of biological mechanisms that switch genes on and off. There are three major levels of epigenetic changes: (1) chemical modification at nucleotide level (DNA methylation and RNA interference), (2) modifications at histone level, and (3) nucleosome remodeling.

Genome-wide association studies (GWAS) Are studies that identify DNA markers (SNPs) in the whole genome that are common to the human genome and to determine how these SNPs are distributed across different populations. GWAS are used to determine genetic risk markers associated with a disorder, for example, diabetes, obesity, hypertension, or cancer.

Glycosylated hemoglobin (HbA1c) Is also known as glycated hemoglobin. The glycation of hemoglobin consists in a nonenzymatic interaction between glucose and the amino groups of the valine and lysine residues in hemoglobin. This interaction is irreversible and is a test that indicates the exposition of the proteins to glucose for the last 3 months.

Knock-out mice Is a model used is the laboratory in which a mouse has inactivated, or "knocked out" an existing gene by replacing it or disrupting it with an artificial piece of DNA.

Maturity-onset diabetes of the young (MODY) Is a rare form of diabetes different from both type 1 and type 2 diabetes and runs strongly in families. Is caused by a mutation in a single gene.

OLEFT rats The Otsuka Long-Evans Tokushima fatty (OLETF) rat is an animal model of spontaneous T2D. This rat model of T2D is characterized by mild obesity with visceral fat accumulation and late-onset insulin resistance. It resembles human obese patients with T2D.

Pathogen-associated molecular patterns (PAMPs) Are derived from microorganisms and recognized by pattern recognition receptor (PPR)-bearing cells of the innate immune system as well many epithelial cells. Major PAMPs are microbial nucleic acids, including DNA, double-stranded RNA (dsRNA), single-stranded RNA (ssRNA), and 5′-triphosphate RNA and lipoproteins, surface glycoproteins, membrane components (peptidoglycans, lipoteichoic acid, lipopolysaccharide, and glycosylphosphatidylinositol).

Promoter The promoters are sequences in the DNA that define the start point in the transcription of a gene.

Reactive oxygen species (ROS) Are radical and non-radical oxygen species formed by the partial reduction of oxygen, for example, superoxide anion (O_2-), hydrogen peroxide (H_2O_2), and hydroxyl radical (HO•). They are generated endogenously by the oxidative phosphorylation process in the mitochondria or are produced from interactions with exogenous sources such as xenobiotic compounds.

Roux-en-Y gastric bypass (RYGB) Is often called gastric bypass and is considerate the "gold standard" of weight loss surgery. This surgery consists to create a new stomach pouch, using a small portion of the stomach. The smallest stomach is connected directly to the middle portion of the small intestine (jejunum), bypassing the rest of the stomach and the upper portion of the small intestine (duodenum).

Single nucleotide polymorphisms (SNPs) Is a variation in a single position in a DNA sequence among individuals.

This variation have to be present in almost 1% of a population to be considered as an SNP.

Streptozotocin (STZ)-induced diabetes Streptozotocin is a glucosamine-nitrosourea compound derived from *Streptomyces achromogenes*. STZ is employed to induce cellular damage specifically in **β**-cells, resulting in hypoinsulinemia and hyperglycemia.

Transcriptomic The transcriptome is the complete set of expression products transcribed from the genome in a specified tissue or populations of cells. Transcriptomic has emerged as a powerful technic that analyses thousands of genes in one sample using RNA microarrays. This technic has allowed the study of gene expression patterns on several tissues involved in the pathogenesis of the T2D and to identify genetic markers for the early diagnosis of T2D.

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The Immune System and Inflammation in Type 2 Diabetes

12

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Objectives

- Obesity-associated inflammation as a major contributor toward the progression to IR and T2D.
- Relevance of adipocytes and some classes of immune cells in obese adipose tissue as mediators of inflammatory state.
- Several proinflammatory markers expressed by immune cells have been considered as potential risk factors for developing T2D.
- Anti-inflammatory therapeutic approaches to alleviate IR and T2D.

Introduction

This chapter focuses on immune cells' participation during type 2 diabetes (T2D) development. Obesity is a major driver of T2D. However, obesity per se does not necessarily lead to T2D, but rather to individual differences regarding body composition, fat distribution, and adipose tissue (AT) function.

Most findings demonstrating the correlation between AT dysfunction and T2D have been observed on mouse models or obese subjects and/or those with impaired insulin sensitivity. It is also known that increasing overweight and obesity incidence have been linked to increasing amounts of T2D cases. It is a well-recognized fact that chronic low-grade inflammation is correlated to obesity-associated comorbidities. Furthermore, adipose tissue (AT) is an important immunologically active organ that contributes during inflammation processes.

The development of T2D results from a combination of insulin resistance (IR) and pancreatic beta-cell failure, thus resulting in hyperglycemia. A chronic activation of the innate immune system is associated with T2D, and there is evidence suggesting that both IR and beta-cell failure are regulated by this inflammatory status in humans [1, 2].

Some intervention studies have shown that therapies for obesity-induced T2D relying on immune markers include those approaches intended to increase insulin sensitivity by blocking the activity of inflammatory mediators, e.g., interleukin (IL)-1α, IL-1β, IL-6, tumor necrosis factor (TNF-α), and macrophage chemoattractant protein 1 (MCP-1) [3, 4].

Increased adipocyte size is associated with a decreased population of precursor cells able to differentiate into adipocytes. Large adipocytes are more frequently found in subjects with impaired glucose tolerance and T2D in comparison to those with a similar degree of adiposity but with normal glucose tolerance. Impaired adipocyte differentiation appears to be one of the most important factors for T2D progression [5]. The presence of proinflammatory cytokines in blood hampers the capacity of the insulin receptor to convey signals within insulin-sensitive tissues.

Insulin has several functions in its target tissues including nutrient transport as well as the regulation of gene expression and energy homeostasis. It acts on a several target tissues and through many different intracellular signaling cascades. Elevated levels of intracellular free fatty acids (FFAs) may blunt the response toward insulin and its subsequent metabolic effects. The insulin receptor substrate (IRS)-1 is a key molecule in this signaling pathway, and failure to activate it leads to systemic IR [6–8]. Inflammatory cytokines such as TNF-α and IL-6 may induce an inhibitory phosphorylation of IRS-1. A similar response is achieved by activating the receptors of the innate immune system, such as the toll-like receptors (TLR) or by the presence of intracellular molecules, e.g., lipids and reactive oxygen species

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(ROS). By interacting with their respective receptors, TNF-α and IL-6 activate the nuclear transcription factor κB (NF-κB) and the Janus kinase (JNK); both of them are important inflammation activators. JNK is also activated by FFAs and endoplasmic reticulum stress. Interestingly, these factors are associated with obesity [9, 10]. The regulator of cytokine function known as the suppressor of cytokine signaling (SOCS) inhibits insulin effects on IRS-1, either by interfering with tyrosine phosphorylation or by targeting IRS-1 for proteasomal degradation [11, 12].

Ectopic lipid accumulation in the pancreas, concomitantly with a decreased activation of the insulin receptor in adipocytes, minimizes insulin production and impairs insulin-stimulated glucose transport, and its anti-lipolytic effect as well as lipoprotein lipase production and activity, whereas it increases the release of FFA and hampers preadipocyte differentiation. All these effects will lead to IR, T2D development, including cardiovascular diseases.

Types of Adipose Tissue

Systemic inflammation induced by obesity is predominantly originated at the AT. Mammalian body contains several types of fat reservoirs, classified as white and brown fat [13]. White adipose tissue (WAT) is in turn classified as subcutaneous (Sc) and visceral adipose tissue (VAT). The former stores the calorie surplus, and it may be further classified as upper and lower body obesity. On the other hand, VAT (omental and mesenteric) supplies energy to all organs. Sc predominates over VAT by a 3–4 factor [14, 15].

WAT stores nutrients within a single large fat droplet. This tissue is one of the main endocrine organs in the organism. VAT is located in the abdominal cavity, it is the main source of chronic systemic inflammation, and it is of outmost importance for T2D establishment [15]. In different mice strains (Kunming, C57BL/6, BALB/c, and ICR) with high-fat diet (HFD), it was observed an increase of body weight and largest adipose cells, and the animals showed altered response on glucose and insulin loads (OGTT and ITT, respectively) [16]. The content of specific immune cells (natural killer (NK) cells) in VAT is modified when obesity develops [17].

Brown adipose tissue (BAT) is mostly found in newborn humans, even though adults possess small amounts of this type of fat. In spite of WAT and BAT sharing many metabolic features, the former stores energy, whereas the latter dissipates energy and produces body heat [13]. In BAT, the signaling mediated by the mammalian target rapamycin complex 2 (mTORC2) stimulates cold-induced glucose uptake and glycolysis. AdRiKO mice, which have deleted mTORC2 in adipose tissue, are hypothermic and show more cold sensibility and glucose uptake and impaired glycolysis [18]. Also, in this tissue, the increase in UCP-1 expression can increase glucose uptake [19].

Ectopic Fat Accumulation

Fat is accumulated in specific regions along the body when obesity develops. Normally, the abundance of AT is low in these zones.

Ectopic fat is defined as a triglyceride deposition within non-adipose tissue cells that normally contain small amounts of fat. The liver, skeletal muscle, and pancreas contain an excessive lipid accumulation. In the skeletal muscle, this fat accumulation is correlated with IR and cardiovascular disease and T2D [20, 21].

Lipid accumulation in the liver and muscle is an early sign of T2D, whereas it has been shown to precede the suppression of glucose-mediated insulin production by the pancreas. In cardiac tissue a lipid overload has been shown to produce a metabolic deregulation, and it may induce IR, resulting in impaired glucose oxidation and, consequently, heart failure [22–24].

Epicardial Adipose Tissue

This specific tissue possesses some anatomical and metabolic features that distinguish it from other visceral fat depots, such as increased fatty acid metabolism and a transcriptome including genes associated with inflammation and endothelial functions. Some bioactive adipokines such as adiponectin, TNF-α, IL-6, and resistin, as well as FFA from epicardial AT may impact on cardiovascular function and morphology. Therefore, they may directly contribute to cardiovascular complications and IR [24, 25].

Perivascular Fat

The perivascular adipose tissue surrounding blood vessels is produced from the vascular lamina adventitia in response to circulating factors and local stimuli. This fat tissue has been considered a largely passive structural support for arteries. Nevertheless, it can play an active role to regulate vascular tone and the release of adipocyte-derived vascular-relaxing factors into the blood vessels. Perivascular adipose tissue contributes to the modulation of vascular tone in vivo [26].

Obesity and Acute and Chronic Inflammation

Inflammation is a series of cellular and molecular responses in order to protect the body from infections or other insults. The inflammation process is continuous over a time period. Acute and chronic are terms used to describe different inflammation stages. This event is triggered by a stimulus and, when it ceases, inflammation is attenuated. If it does not remain in the acute period, it becomes chronic.

When compared to acute inflammation induced by bacteria or viruses, chronic inflammation may be driven by an abnormal reaction toward the presence of endogenous factors, including metabolic factors such as advanced glycation end products (AGES), modified lipoproteins, type 2 T helper cells (Th2), cytokines, hyperglycemia, and others [27–29].

Monocytes, one of the key cell types on the innate immune system, recognize the presence of these factors in the bloodstream, they migrate to the respective tissues, and they may recruit macrophages with pathological functions. Obesity-associated inflammation is characterized by an increased amount of macrophages and proinflammatory cytokines in the AT.

It was been shown that one type of monocytes (CD16+) was increased in patients with metabolic disorders, and it positively correlates with body mass index, insulin resistance, diabetes, and intima media-thickness. Likewise, the percentage of nonclassical monocytes was increased in individuals with obesity compared to lean subjects and showed an imbalance among CD16+ monocyte subsets. After high-intensive training, the percentage of nonclassical monocytes was reduced, and the balance among CD16+ monocytes was restored. In another study it was reported that higher account of intermediate monocytes subset (CD14++CD16+) was associated with CVD risk [30, 31].

Inflammation is the response of the living tissue toward injury. It involves a well-organized cascade of humoral and cellular changes within living tissues. Blood is the primary delivery system for inflammatory components such as adipokines TNF-α, IL-6, leptin, resistin, and adiponectin.

Obesity and its associated metabolic pathologies, such as IR, T2D, and atherosclerosis, are chronic and concomitant associated with inflammatory responses such as increased acute-phase reactants as the C-reactive protein (CRP), activation of inflammatory signaling pathways, high levels of circulating inflammation biomarkers as interleukin (TNF-α, IL-6, IL-1β, plasminogen activator inhibitor-1 (PAI-1)), and low adiponectin levels (an anti-inflammatory adipokine). The latter may predict the future establishment of T2D. The inflammatory response is mainly located in adipose tissue, and it is triggered therein, although other tissues may be involved when T2D is developing [32, 33].

In the AT, immune cells participate on tissue remodeling and homeostasis, and these roles are controlled by inflammation. AT is considered a complex endocrine tissue containing multiple cell types, including its precursors, vascular, immune, and neuronal cells. All of them contribute to the inflammatory response occurring in obesity. A nutrient excess promotes adipocyte expansion, resulting in its dysfunction. Cytokines, chemokines, and adipokines secreted by adipocytes induce immune cell accumulation in the AT and trigger local and systemic inflammation, being one of the causes contributing to IR [34].

Type 2 Diabetes and Immune Cells

The immune response has been classified as innate and adaptive. The former represents a rapid response toward some stimuli, and it is characterized by physical, chemical and biological barriers, specialized cells, and soluble molecules. They occur in all individuals, regardless of their previous contact with harmful agents or immunogens, and they do not qualitatively or quantitatively change after contact [35].

The human leukocyte antigen (HLA) constitutes a system also known as the major histocompatibility complex MHC. This is a protein set derived from highly polymorphic genes linking innate and adaptive responses. The human genes are allocated in classes I, II, and III. Only those of classes I and II participate to present antigen proteins to T cells. All MHC molecules found on the cell's surface contain an associated peptide.

Those from class I possess one α-chain coded by the HLA-A, B, or C genes and a small non-variable chain: the β2-microglobulin. HLA class II possess two chains: α and β. HLA discriminates between intrinsic and foreign elements, and they ensure a suitable immune response in order to protect against external agents capable to generate an infection.

Adaptive or acquired immune response depends on the activation of specialized cells and the soluble molecules produced by them. The main features of the acquired response are memory, specificity and diversity of recognition, self-restraint, specialized response, and tolerance to the components of the organism itself. The cells that are mainly

involved on the acquired immune response are lymphocytes. Antigen-presenting cells (APCs) play a key role during lymphocyte activation by presenting them with antigens bound to the major histocompatibility complex (MHC) molecules [36, 37]. Type-T lymphocytes recognize antigenic fragments derived from pathogens that previously entered the cells but only when associated with the major histocompatibility complex proteins. In humans, the latter is termed the human leukocyte antigen (HLA). Concomitantly with the innate immune system signs, it triggers the T-cell-mediated immune response [38].

Macrophages, neutrophils, dendritic cells, and natural killer (NK) cells are the main effectors of innate immunity. The central mechanisms of innate immunity comprise phagocytosis, the release of inflammatory mediators, activation of the complement system proteins, and the synthesis of acute-phase proteins, cytokines, and chemokines. These are activated by specific stimuli, such as the lipopolysaccharides commonly found on the outer membrane of microorganisms [35].

AT is comprised by mature adipocytes (≈50%) and other cells (≈50%) from the stromal vascular fraction (SVF) that contains pre-adipocytes, fibroblasts, endothelial cells, and immune cells, e.g., macrophages [39].

After analyzing several adipose reservoirs, it was observed that immune cells represent approximately two thirds of the SVF, containing approximately 2–5 million cells/g of tissue. In morbidly obese subjects, AT represents up to 50% of total body mass, and it is the main compartment of the immune system having an effect on systemic inflammation [40].

Cell populations within the AT display a plasticity that is regulated by both acute and chronic stimuli including body weight status, diet, feeding, and fasting. Mice fed with a HFD recruit immune cells (such as T and B cells, M1 phenotype macrophages) to AT [41, 42].

Obesity and insulin resistance are concomitant with macrophages infiltrating the AT [42]. In addition to these, other immune cell populations change in obese AT, and they affect insulin sensitivity. Some of them have an impact on inflammation by altering AT-macrophage recruitment or activation. Lean AT also contains regulatory cells such as eosinophils and invariant natural killer (iNK) cells. These preserve tissue homeostasis by excreting two types of cytokines, such as IL-4, IL-5, and IL-13, whereas they keep AT-macrophages in an anti-inflammatory status (M2). When diet-induced obesity develops, AT homeostasis is disrupted and a type 1 inflammatory response in VAT is engaged. This is characterized by the presence of interferon gamma (IFN-α), a shift toward a proinflammatory profile (M1) by most of the recruited macrophages and the loss of regulatory T cells (Treg) [43]. Further sections show the interrelation of major immune cells and obesity-related T2D.

Macrophages

In vertebrates, innate immunity greatly depends on myeloid cells as they engulf and destroy pathogens. Mononuclear phagocytes, macrophages derived from blood monocytes, and polymorphonuclear phagocytes are comprised within myeloid cells. Macrophages are distributed throughout the body, and in some cases they are located within the parenchyma of some major organs (e.g., heart, brain, lungs, and liver), adopting diverse morphologies such as spindle-shaped tissue histiocytes, Küpffer cells of hepatic sinusoids, and stellate microglial cells of the central nervous system. Macrophages are within the periphery of invasive organism or at the site where a chemical or biological insult occurs. As such, they are also involved on IR, T2D, and atherosclerosis development [44].

> Histiocytes are derived from the bone marrow; they circulate throughout the body to subsequently infiltrate some organs where they undergo differentiation into histocytes (e.g., macrophage or dendritic cells).

In lean mice, approximately 10–15% of all cells express the macrophage marker F4/80+, whereas they constitute about 45–60% of cells in adipose tissues of obese animals. This indicates that obesity significantly modifies the macrophage/adipocyte ratio. Macrophages are normally located in lean AT in which they participate in normal remodeling, they are the primary source of TNF-α significant amounts of inducible nitric oxide synthase and IL-6. Nutrient overlap triggers AT remodeling and inflammation in this tissue. Macrophage-specific gene expression is markedly upregulated in WAT from obese mice. When diet-induced obesity occurs, this phenomenon precedes to an increase of circulating insulin levels [45, 46].

The macrophage proportion on the SVF is estimated to increase from ≈10% in lean conditions to ≈40–50% in obese AT. Furthermore, obesity induces a macrophage phenotype switch from M2 (producing anti-inflammatory cytokines as IL-10) to the M1 type (producing proinflammatory cytokines as IL-12, inducible nitric oxide synthase, and major histocompatibility complex class II). The latter is associated with IR in both mice and humans. Endoplasmic reticulum stress or hypoxia may contribute to the M2-M1 transition of macrophages. In addition to increase inflammatory responses, the factors released by macrophages also modulate adipokine production, and they inhibit adipogenesis [1, 47–55].

Infiltration of proinflammatory macrophages in association with obesity do not only occur in WAT but also on the skeletal muscle, bone (osteoclasts), liver (Küpffer cells), and pancreas. In the latter, they contribute to IR and to β-pancreatic cells dysfunction by activating inflammatory

processes [56–59]. During T2D development, macrophage recruitment seems to occur in several tissues, implying a general inflammation status rather than a WAT-specific inflammation.

Mast Cells

Mast cells contribute to antimicrobial defense by secreting granules rich in histamine, serine proteases, and cytokines, mainly TNF-α and IL-1β. These cells have a role in anaphylaxis and allergy. In obesity models fed with a HFD, mast cells are recruited to AT, and they contribute to inflammation, whereas they participate in IR by secreting inflammatory cytokines [60]. Mast cell deficiency in diet-induced obese mice protects from weight gain and IR, possibly due to a decrease of inflammatory cytokines, MCP-1, and matrix metalloprotease-9 in both VAT and serum [61]. Additionally, human mast cells cultured in vitro in the presence of high glucose levels are activated and highly express proinflammatory cytokines, including TNF-α, IL-1β, and IL-6 [62]. Nevertheless, a recent work has presented contradictory conclusions regarding mast cell involvement in IR, as phenotypes may be more dependent on the Kit mutation used in those mouse models rather than a mast cell deficiency per se [63]. WAT obtained from morbidly obese patients displays a mast cell increase regardless of IR. Furthermore, mast cells do not contribute neither to inflammation caused by obesity, glucose intolerance, or IR, as these were observed on mast-cell-deficient mice with diet-induced obesity [64].

Eosinophils

The stromal vascular fraction (SVF) of lean AT contains eosinophils, although they rapidly decline during obesity onset, as shown in a DIO model. In the lean state, eosinophils repress AT inflammation by producing IL-4, a key driver of alternative M2 macrophage polarization in order to preserve a "lean phenotype." When fed with a HFD, eosinophil-deficient mice exhibit a significant weight gain, impaired glucose tolerance, and IR. Conversely, transgenic mice engineered to contain high eosinophil levels were protected against obesity and IR when a HFD was supplemented. This highlights the importance of eosinophils in order to prevent IR [46, 65].

Lymphocytes

A lymphocyte is a white blood cell that triggers an immune response when activated by a foreign molecule (antigen). The different T lymphocyte types are distinguished by a differential expression of their transmembrane proteins or co-receptors known as CD. T lymphocytes are generated in the thymus, and they are responsible for cell-mediated immunity. They comprise innate (γδ T, NK) and adaptive immune (CD4+, CD8+ T lymphocytes, and B lymphocyte) cell subpopulations. CD4+ T lymphocytes are further sub-classified as T helper (Th) type 1 (Th1) (they secrete IFN-γ and IL-2), Th2 (they secrete IL-4, IL-5, and IL-13), Th17 (a subset of Th CD4 cells that mainly express IL-17, IL-21, and IL-22), and T regulatory cells (Treg). Th cells display the CD28 co-receptor on its surface. Additionally, activated Th cells express a CD40 ligand on its surface, but not in their nonactivated form [66, 67].

In adult animals, T and B lymphocytes in secondary lymphoid organs are comprised by a mixture of cells in at least three maturation stages. They are designated as virgin (or naïve cells), memory cells, and activated cells. When virgin cells are exposed to an antigen for the first time, some of them are stimulated in order to multiply and mature to become activated cells. These are defined as those cells engaged in a response (activated T cells carry out cell-mediated responses or they secrete mediators, whereas activated B cells secrete antibodies) [68, 69].

During the inflammatory events occurring in obesity, IR, and T2D, some lymphocyte subpopulations display abnormalities. In patients undergoing T2D onset, IL-22(+) CD4(+) T cell populations were higher when compared to healthy individuals, and they may contribute to the early stages of the disease. Proinflammatory γδ T, Th1, and CD8+ T cells were increased in response to a HFD [39, 70]. Ketogenic diet feeding in mice causes obesity, impairs metabolic responses, and depletes the adipose-resident γδ T cells; these cells are mediators of protective immunometabolic responses that link fatty acid-driven fuel use to reduced adipose tissue inflammation [71]. Th1 and Th17 cells expressed the IFN-γ and IL-17 proinflammatory cytokines, previously associated with IR [72–74]. NK cells were positively associated with glucose levels, glycated hemoglobin (HbA1c), and in women with morbid obesity and varying levels of IR [75]. Differentiation of Treg and Th17 cell are events that often counteract each other, whereas Treg cell abundance is decreased in obesity [74].

The amount of CD4+ and CD8+ T cells increased in VAT in response to diet-induced obesity (DIO) [73]. In diet-induced obesity (DIO), adiponectin, an anti-inflammatory adipokine, inhibits IFN-γ and IL-17 production from CD4+ T cells. CD8+ T cells promote macrophage recruitment mediated by MCP-1 production, and its deletion significantly decreases systemic inflammation and IR in mice submitted to DIO [73, 76, 77].

Immune cells may increase glucose utilization during diabetes progression. Possibly they control their own activation and polarization in order to acquire proinflammatory pheno-

types. For instance, T helper 17 (Th17) cells are dependent on glycolysis, and its inhibition shifts T-cell differentiation from proinflammatory Th17 cells to anti-inflammatory Treg cells. Similarly, glucose metabolism is required by mouse macrophages in order to secrete IL-1β [78, 79].

In mice receiving HFD, the CD8+ effector T cells and proinflammatory macrophages infiltrating adipose tissues were increased, and Treg was reduced in both AT and the liver. These mice under weight loss improve their metabolic profile and increase CD4+ T, but they showed an active CD8+ T cell inflammation mediated by macrophages in AT and the liver, and Treg remained low [73, 80].

In T2D patients the Treg/Th1 and Treg/Th17 ratios significantly decreased when compared to healthy controls. T2D patients with coronary heart disease (CHD) showed a significant decrease of Treg/Th1 regarding T2D patients without a CHD diagnosis [81]. Subsequently, AT in obesity conditions exhibit some typical symptoms of chronic inflammation, thus leading to systemic IR, T2D, and cardiovascular diseases.

Mice under HFD treated with pioglitazone, a PPAR-γ agonist, showed an increase of the number of Treg cells in AT along with decreased inflammation. In obesity conditions Treg may be critical regulators of immune cell components in VAT. The evidence reveals that their modulation may represent a potential novel strategy to treat obesity-related metabolic disorders, such as IR and T2D [82, 83].

B Cells

In mammals, B cells or B lymphocytes are produced in the bone marrow, and they secrete circulating antibodies. B cells are responsive to bacterial products such as lipopolysaccharide (LPS), and thus they are considered one of the first lines of defense against bacterial pathogens. Similar to T cells, B cells are comprised by different subsets with distinct surface phenotypes, functions, and cytokine secretion profiles. B cells may be classified in two broad types: B-1 or B-2 cells based on their development, phenotypes, functions, and cytokine secretion profiles [84].

B-1 cells have been found in fatty tissues such as omentum, the fat pads near the peritoneal cavity, and in mucosal tissues. B-1a cells are major producers of natural IgM antibody, and they are responsible for adaptive humoral immune responses toward T cell-independent antigens. In the steady state, there is constant B-1 cell trafficking between the peritoneal cavity and the abdominal VAT, such as the omentum [85–87].

B-cell populations infiltrate inflamed tissues such as VAT in mice fed with a HFD, and they subsequently undergo functional and phenotypic changes. B-cell infiltration is thought to precede that of T cells into VAT. Once in there, they may regulate systemic and local inflammation, concomitant with antibodies and cytokines secretion. Similar to macrophages, B cells express the major histocompatibility complex II (MHCII), and they possess the ability to present antigens to T cells [88–90].

B-2 cells produce several cytokines, and some populations are able to produce proinflammatory cytokines such as IFN-γ, IL-12, and TNF-α, whereas other populations produce IL-2, IL-4, and IL-13. More recently, the presence of regulatory B cells ("Breg" cells) that possess the ability to suppress inflammatory responses has been described. One subset of these includes a type of B cells termed "B10" that produce a high amount of IL-10 [91, 92].

B cells may modulate T cell and macrophage polarization and cytokine production at multiple levels; thus, they represent a potential attractive target for immune therapy to treat insulin resistance. During the early stages of the disease, the depletion of B-cell co-receptor caused by a CD20 antibody induce a therapeutic and beneficial effect on glucose metabolism. Additionally, T-cell activation was hampered, and both IFN-γ and TNF-α levels were decreased in VAT. Conversely, detrimental effects on metabolic disease are mediated by B cells by producing pathogenic IgG [93–95].

Natural Killer T Cells

Natural killer (NK) T cells are a subtype of innate T lymphocytes, they exhibit both innate and adaptive features, and they mediate the consequent immune responses. NK cells are the body's sentinels searching for signs of cellular stress, activating the immune system in response to viral infection or oncogenic transformation. They recognize peptides presented by the MHC molecules. NK cells also recognize lipids presented by CD1d molecules. The latter is a non-polymorphic MHC class I-like molecule that is mainly expressed by dendritic cells (DCs) and other cell types. NK lymphocytes are classified in three groups: invariant (iNK), type II, and NK-like lymphocytes, based on their antigen specificity and the expression of their T-cell receptor (TCR). NK cells are located within the AT. It has been recently shown that NK cells are associated with obesity and diabetes. In several obesity models and in obese patients, NK cells are increased, and they drive proinflammatory M1 macrophage polarization mediated by IFN-γ production, and subsequently they promote IR [96–98].

When activated, NK cells promote the death of a target cell by releasing cytolytic granules [86]. NK cell activity is controlled by the balance of signals received from receptors on the cell's surface that convey either activating or inhibitory signals [99]. Under normal physiological conditions, NK cell activation is inhibited by ligands expressed by healthy cells that engage the inhibitory NK receptors. In

stressed cells the expression of these ligands is decreased, leading to NK cell activation. Furthermore, diet-induced IR may be delayed by preventing NK cell activation using a soluble NK cell-activating receptor (NCR1). Mice fed with a HFD exhibit an increased number of NK cells concomitantly with an enhanced production of proinflammatory cytokines, particularly TNF-α in epididymal but not in subcutaneous fat depots. Additionally, NK cells are an important source of IFN-γ in VAT [100].

Invariant Natural Killer T

iNKT cells are a specialized subset of innate T cells highly abundant in the liver, and they are readily activated by lipid antigens. These cells are potent transactivators of other immune cells, and they serve as a bridge between innate and adaptive immunities. They are highly conserved in mammals, they are part of human and murine AT, and they display a unique phenotype characterized by a surface marker. iNKT recognize glycolipids presented by CD1d, and they participate to preserve AT homeostasis through both immune and metabolic pathways. These cells have an anti-inflammatory role in VAT as they produce IL-4 and IL-2. In obese patients iNKT cells are decreased when compared to lean controls. This effect has been also observed in DIO and genetic obesity models. The activation of iNKT (iNKT10) cells mediated by the lipid agonist α-galactosylceramide (αGC) led to macrophage polarization to a M2 phenotype, and it improved glucose sensitivity through anti-inflammatory cytokine signaling. Furthermore, the number of iNK cells is recovered after weight loss, whereas proinflammatory macrophage infiltration is decreased [101–103].

The decreased amount of iNKT cells in the liver of obese mice contribute to hepatic IR. Conversely, their increase in obese liver results in improved hepatic steatosis and glucose tolerance [104].

iNKT cells are linked to obesity-induced IR [102]. However, the role of iNKT cells during HFD-induced inflammation and IR is still controversial, because in vitro studies showed that iNKT cells display considerable plasticity with respect to their cytokine output, which can be skewed toward a more proinflammatory profile [105, 106].

iNKT cells are decreased in obesity, although their activation leads to improved glucose control, insulin sensitivity, and even weight loss, and they represent a therapeutic possibility to restore homeostasis in obese adipose tissue [107].

Dendritic Cells

There are three subpopulations of dendritic cells (DC): myeloid, CD4+, and CD8+. DCs play an important role for the transition between innate and adaptive immunity by presenting antigens to the T-cell receptors (TRs) of CD4 Th cells via MHC II. In AT of obese animals, macrophages and dendritic cells (MDC) increased and display the classically activated M1-like phenotype in obese adipose tissue (AT) and may contribute to AT inflammation and insulin resistance. Murine adipose tissue contains a novel CD11c+ dendritic cell subset that is distinguished by an immature phenotype. AT from mice fed with an HFD contained an increased number of CD11c+ DCs and CD4+IL-17+ T cells regarding lean controls. A link between CD11c+ DCs and AT inflammation caused by Th17 cells may exist in obesity conditions [108–110]. In obese patients, the frequencies of DCs, Th1, and Th17 cells increased, and Treg and Th2 cells decreased compared with normal controls. The frequency of DCs and Th1 cells consistently declined after laparoscopic sleeve gastrectomy surgery, while Th17 cells declined at 6 months after surgery compared with baseline in the same obese patients [111].

Markers of Inflammation

T2D as an inflammatory process is concomitant with increased levels of circulating proinflammatory immune mediators that lead to impaired insulin signaling and the selective destruction of insulin producing β-cells, a process in which cytokines play an important role. Generally, some of the inflammatory markers playing a pathogenic role in T2D are expressed in both adipocytes and immune cells. Among these are proinflammatory molecules as TNF-α, IL-1β, 4, 6, 18, resistin, and leptin. Anti-inflammatory molecules are also involved such as the IL-1 inhibitor or IL-1 receptor antagonist A (IL-1RA), transforming growth factor-β1 (TGF-β1), IL-10, and adiponectin [112, 113].

Regarding the activation status of WAT macrophages, mice with DIO display a M2 to M1 shift, as previously indicated. The former is characterized by the expression of anti-inflammatory cytokines (e.g., IL-10, IL-1Ra), whereas the latter are distinguished by an elevated production of proinflammatory cytokines (e.g., TNF-α and IL-6) [114].

Some of the proinflammatory and anti-inflammatory proteins have been implicated in obesity, IR, and T2D, and their respective functions are described below.

The cytokines expressed by adipocytes and immune cells, such as TMF-α, IL-1β, and IL-6, either impair insulin signaling or induce β-cell apoptosis [115, 116]. TNF-α and IL-18 are considered potential risk factors for T2D development and its associated metabolic complications [117, 118].

TNF-α

TNF-α is a classical proinflammatory cytokine that actively participates during the development of obesity-related diseases. It is secreted by mature adipocytes, although it is also expressed by macrophages. It has been implicated in obesity and T2D development. The expression of TNF-α mRNA increases in AT reservoirs, and it correlates with IR, body mass index, percentage of body fat, and hyperinsulinemia. A short-term treatment with a TNF-α inhibitor decreased systemic inflammatory markers without improving insulin sensitivity in obese patients. The serum levels of this cytokine diminishes after weight loss in obese subjects. Moreover, anti-TNF-α antibody reduces IR in rats with sepsis-induced stress hyperglycemia. Besides, a novel inhibitor JTP-96193 was reported that acts on the TNF-α converting enzyme/a disintegrin and metalloproteinase domain-containing protein 17 (TACE/ADAM17), which is a key sheddase that releases TNF-α from its inactive precursor and is a new drug to inhibit TNF-α production. This inhibitor will become a new treatment option of T2D [119–122].

In vivo studies with mouse models clearly show that inhibition of TNF-α function improves obesity-induced inflammation. High TNF-α levels were also found in the AT from obesity experimental models: rat (fa/fa), mouse (ob/ob), and mice fed with HFD. In obese fa/fa rats, the impairment of TNF-α expression increased insulin effect on glucose uptake. Similar results were observed in two murine obesity models: significantly improved insulin sensitivity was detected in animals lacking TNF-α or its receptors when compared to their obese wild-type counterparts. The mechanisms underlying insulin resistance mediated by TNF-α may involve the phosphorylation of insulin receptor substrate (IRS)-1 on its serine residues, as they inhibit normal phosphorylation of IRS-1 on tyrosine residues, thereby blocking insulin signaling. TNF-α downregulation, in HepG2 cells, improves IRS-1 phosphorylation after insulin stimulation [123–125].

TNF-α contributes to the development of peripheral insulin resistance on AT and the liver by stimulating lipolysis mediated by cyclic adenosine monophosphate (cAMP) and by stimulating the activity of the hormone-sensitive lipase. In WAT, TNF-α induces a decrease of lipoprotein lipase as well as GLUT-4 expression and activity. In the liver, TNF-α stimulates the expression of genes involved in cholesterol and FA de novo synthesis, whereas it inhibits those genes involved in glucose uptake and metabolism as well as FA oxidation. The effects promoted by this cytokine on lipid metabolism result in high FFA plasma levels, fatty acid deposition in non-adipose fat reservoirs, including muscle. Therefore, they might contribute to IR observed in obesity [126, 127]. TNF-α increases acyl-CoA synthesis by induction of acyl-CoA synthetases in human macrovascular endothelial cells. TNF-α-mediated processes may be involved in complications associated with T2D such as cardiovascular disease [128].

IL-1β

IL-1 family is a group of cytokines that play a central role to regulate immune and inflammatory responses. Additionally, other circulating inflammatory markers and high IL-1β levels have been reported on humans with IR [129, 130].

IL-1β may drive sterile inflammation, and it is considered a metabolic disease initiator in T2D patients and in animal models with T2D. Studies conducted on humans and animals have found that IL-1β or inflammasome (a complex required for the IL-1β secretion) is increased in metabolic diseases. Moreover, treatment with IL-1β antagonists can improve glycemia. Pancreatic β-cells in mice (db/db) and rat beta cell line (INS-1) are able to produce the proinflammatory cytokine (IL-1β) when cultured in the presence of high glucose levels, thus impairing β-cell function and inducing apoptosis. In a clinical trial, it was observed that the administration of anakinra, a recombinant human IL-1-receptor antagonist (IL-1Ra) improved glycemia on rheumatoid arthritis with comorbid T2D patients [131, 132].

IL-1β interferes with insulin signaling in both adipocytes and hepatocytes, it suppresses insulin-induced glucose uptake, and it inhibits lipogenesis and decreases adiponectin release [131, 133]. Some contradictory results have been observed on pancreatic β-cells, low IL-1β doses improve insulin secretion, enhance β-cell replication, and decrease β-cell apoptosis. Conversely, high IL-1β levels induced by high glucose and/or FFA levels have the opposite effects on islets [134, 135]. These effects must be taken into account, as possible diabetes treatments using IL-1β blocking as a strategy may cause a severe abrogation of its signaling pathway that will have severe consequences and they may compromise insulin secretion even further in patients with severely damaged or destroyed beta cells.

The pancreas from T2D and obese patients, but not from control subjects, expresses IL-1β [58]. IL-1β promotes β-cell dedifferentiation in cultured human and mouse islets, and in vivo, anti-IL-1β treatment improved insulin secretion of isolated islets [136]. In T2D patients, NLRP1 inflammasome expression was upregulated in islet cells, suggesting that IL-1β causes β-cell toxicity in part by NLRP1-mediated caspase-1-activation [137].

IL-6

IL-6 is a single polypeptide chain comprised by 185 amino acids; its molecular weight ranges from 21 to 28 kDa depending on its phosphorylation and glycosylation status. It is a pleiotropic cytokine secreted by a wide variety of cells: endothelial cells, β-pancreatic cells, keratinocytes, osteoblasts, myocytes, adipocytes, fibroblasts, activated leukocytes, monocytes, macrophages, and other cells, including a few tumor cells [138]. IL-6, expressed by type 2 T helper cell (Th2), specifically regulates the Th1/Th2 balance [139].

The main progression step toward T2D is insulin resistance, and it has been linked to increased circulating cytokine levels. One of them is IL-6, an inflammatory marker induced by TNF-α in cultured subcutaneous adipose cells. High IL-6 levels have been correlated with IR [140, 141]. Additionally, IL-6 serum levels increase in T2D, in mice with DIO and in obese individuals [139, 142]. IL-6 is an important inflammation mediator, and it has an essential role during the acute phase of the inflammatory response by stimulating CRP synthesis in the liver [143].

The basal circulating IL-6 levels are released from the subcutaneous AT in healthy humans, mainly from macrophages [144, 145]. Human subcutaneous AT expresses both TNF-α and IL-6, but only IL-6 is released from this tissue. IL-6 increases with adiposity and is greater in obese compared with lean subjects. These facts contribute to a chronic low-grade inflammation status in obesity [146, 147].

IL-6 in obesity is generally considered to be a proinflammatory mediator, and it antagonizes insulin action by inhibiting insulin-stimulated glucose transport [147, 148]. Mice deficient in IL-6 develop obesity that is associated with altered carbohydrate and lipid metabolism; IL-6$^{-/-}$ mice showed similar metabolic phenotypes as wild-type mice on a HFD, since these mice had similar expression profiles of lipid-related genes in adipose tissue and the liver [149]. Nevertheless, deletion of IL-6 from adipocytes did not have any effect on glucose tolerance or fasting hyperinsulinemia; adipocyte-specific IL-6 does not contribute to whole-body glucose intolerance in obese mice [150].

IL-6 functions are a consequence of its interaction with its receptor, comprised by the gp130 and IL-6R subunits. IL-6 may directly bind to this receptor complex, or it can bind to a soluble form of gp130 in order to be presented to cells expressing only IL-6R. In this regard, macrophages express high levels of this receptor. IL-6 bound to gp130 has an important participation for macrophage accumulation in AT [131, 151, 152]. Conversely, IL-6-deficient mice develop late-onset glucose tolerance. IL-6 also stimulates the expression of the IL-4 receptor (IL-4R) on macrophages, thereby promoting M2 polarization. Thus, IL-6 appears to function as anti-inflammatory mediator by preventing M1 macrophage formation in homeostasis. Therefore, IL-6 effects for T2D development seems to be time- and concentration-dependent [153].

The presence of IL-6 has been shown to correlate with a higher risk of vascular complications or mortality in T2DM, probably because of its involvement regulating lipid metabolism and CRP production, both of them recognized risk factors for cardiovascular disease (CVD) [154]. IL-6 is also linked to risks of cardiovascular events only in T2D patients with renal dysfunction. In addition, IL-6 levels showed a significant correlation with macrovascular complications in T2D patients [155].

IL-6 mediates several steps during the activation of inflammatory responses by regulating proinflammatory cytokine synthesis. However, it also promotes anti-inflammatory cytokines such as IL-1Ra and IL-10. Obese mice, after acute administration of IL-6, showed improved glucose tolerance, decreased hepatic gluconeogenic gene expression, and increased hepatic phosphorylation of AKT [156]. An acute transient IL-6 increment along with other inflammatory markers also occurs during physical activity, concomitantly with their release [136]. High-intensity interval exercise caused a significant increase in IL-6 and was greater than what was shown under low-intensity exercise of the same duration [157, 158]. Mice submitted to an intensive treadmill running protocol showed high levels of inflammatory cytokines such as IL-1β, IL-6, and TNF-α in serum and skeletal muscle samples [159]. Plasma IL-6 concentrations increased approximately 100-fold during exercise, and the extent of such increase depends on its duration and intensity [160]. IL-6 is required for exercise to reduce visceral adipose tissue mass [161]. In this case, the transient IL-6 increase does not have negative effects on tissues, and the endogenous upregulation of this cytokine in response to exercise improves insulin sensitivity. Therefore, IL-6 exhibits dual properties.

IL-18

IL-18 is a member of the IL-1 cytokine family. It is produced by several hematopoietic and non-hematopoietic cells. IL-18 was identified in human atheroma tissues, and it is an important regulator of innate and acquired immune responses. It induces the expression of several inflammatory molecules in vascular smooth muscle, endothelial cells, and macrophages. The regulation of IL-18 synthesis, its effect on cytokine release, and its mechanisms are still unknown [162].

IL-18-deficient mice develop obesity as a consequence of increased food intake. They also developed insulin resistance in the liver, muscle, and adipose tissue because of an enhanced glucose production. Replacement of IL-18 in brain reduced food intake and reversed hyperglycemia [163]. In American lifestyle-induced obesity syndrome (ALiOS) mouse model, IL-18-deficient mice were protected from early liver damage, possibly due to silencing of the proinflammatory gene expression pattern by NLRP3 activation and IL-18R-dependent signaling [164].

In addition to its role during the inflammatory response toward microorganisms, IL-18 is an important factor in human autoimmune and metabolic diseases. IL-18, IL-4, and IL-12 were significantly higher in diabetic patients regarding healthy subjects. High serum IL-18 levels were correlated with poor glycemic control (assessed as posprandial glucose), prolonged diabetes, and atherogenic index. Furthermore, IL-18 may be used as a predictor for pre-clinical atherosclerosis and poor glycemic control in T2D [165, 166].

IL-18 is considered a potential risk factor for T2D and its associated metabolic complications. In T2D patients serum

levels of IL-18 and its receptor IL-18R are significantly higher than the controls [167]. In obese individuals, the adipose tissue IL-18R/IL-18 expression is enhanced and is associated with proinflammatory gene signature and insulin resistance [168, 169]. IL-18 has been directly implicated in renal injury induction on diabetic nephropathy [170]. IL-18 was also independently correlated with MetS, a known risk factor for CVD, after considering body mass index, lipids, and fasting blood sugar [171]. A prospective study showed that IL-18 was correlated with coronary events in males, regardless of age, body mass index, inflammatory biomarkers, and classic lipid predictors [172, 173]. Mice with an activating mutation in NLRP1, and hence increased IL-18, show decreased adiposity, and they are resistant to diet-induced metabolic dysfunction [174].

TGF-β1

Initially, TGF-β is produced as an intracellular inactive protein complex that is modified before its secretion. One of the most relevant modifications is the C-terminal pro-region cleavage from the N-terminal. The pro-region is known as the latency-associated peptide (LAP), whereas the N-terminal region is the mature or active TGF-β. The latter belongs to a molecule family displaying a variety of roles in several cell types. More than 40 protein members of this family are known, they have a dimeric structure, and they are clustered in several subfamilies. The TGF-β subfamily includes six isoforms; three of them are expressed in mammals [175, 176]. Among these, TGF-β1 is involved in embryogenesis, and it has a prominent role in the immune system by controlling several aspects of inflammatory responses and T-cell differentiation, switching between B-cell isotypes.

TGF-β and retinoic acid are produced by CD103+ DCs located at the small intestine, and they are inducers of Treg cells. TGF-β also induces naive T-cell differentiation into pathogenic TH17 cells while inhibiting the generation of Th1 and Th2 cells in response to immune challenges. Animal models of pancreas-specific overexpression of TGF-β have shown that this factor inhibits diabetes development [177, 178].

TGF-β1 is synthesized as a precursor protein. As it has been associated with the pathogenesis of numerous diseases, the multiple mechanisms of latent (L)-TGF-β activation represent an opportunity to control TGF-β activity within an organ involved in a specific disease process. It is difficult to retrieve reliable epidemiological data on TGF-β1 as it circulates in the bloodstream mainly as its latent form that needs to be proteolytically modified to its active form [179].

In the MONICA/KORA study, high serum TGF-β1 levels were correlated with a high risk of T2D, after adjustment for age, sex, BMI, lifestyle factors, hypertension, lipids, and parental diabetes history [180].

Human islets undergoing β-cell apoptosis is associated with increased levels of TGF-β1; genetic or pharmacologic inhibition of TGF-β/Smad3 signals protects from β-cell apoptosis in mice [181]. Moreover, TGF-β1/Smad3 signaling pathway promotes hepatic gluconeogenesis, both upon prolonged fasting and during T2D. In contrast, genetic and pharmacological inhibition of TGF-β1/Smad3 signaling suppressed endogenous glucose production [182].

Resistin

Resistin was discovered in 2001; it is a small peptide (12.5 kDa) comprised by 108 amino acids containing several cysteine residues. It is a member of a small family of secreted proteins characterized by a unique spacing of 10–11 cysteine residues on their structure. They are known as Resistin-like molecules (RELMs) or as found in inflammatory zone (FIZZ) proteins. Resistin is a cytokine almost exclusively expressed in white adipocytes in rodents, whereas human resistin is predominantly expressed in macrophages, and it is regulated by the nutritional status. It is also expressed by the non-adipocyte stromal vascular fraction in WAT, fibrotic liver, and also on atherosclerotic lesions [183].

Resistin levels are decreased in adipose-derived mesenchymal stem cells differentiation by inducing insulin resistance, and it represents a link between obesity, insulin resistance, and T2D. The antidiabetic drugs thiazolidinediones (TZD) downregulate human resistin expression in macrophages, or they induced a decrease of resistin levels in serum [184, 185].

In obese mice models, circulating resistin levels are higher when compared to lean controls [186]. The administration of exogenous resistin or its transgenic overexpression leads to decreased insulin sensitivity. Conversely, blocking resistin activity or by genetically decreasing its levels improves insulin sensitivity and restores glucose [187, 188].

There are contradictory reports regarding the correlation between resistin and obesity or between resistin and T2D in humans [189–191]. Some reports show that resistin levels are higher in subjects with T2D, but other studies show no correlation with IR or fasting insulin levels [192]. Serum resistin does not change significantly between obese and normal children, and it is not affected by body mass index over time; pubertal girls' resistin levels are not associated with obesity [193, 194].

On the other hand, resistin levels were correlated with increased risk for T2D, even after adjusting for known diabetes risk factors in three large American case-controlled studies (Nurses' Health Study and both the Women's Health Study and the Physicians' Health Study) with follow-ups after 12, 10, and 8 years [195]. Also, higher resistin concen-

tration (above 11 ng/mL) is associated with reduced survival in T2D [196].

Resistin has important roles in CVD and atherosclerosis. Resistin promotes human macrophage proinflammatory polarization and induces further resistin production and secretion in human macrophages [197].

Additionally, resistin also stimulates endothelial cells to secrete substances such as inflammatory cytokines, monocyte chemoattractant protein-1 (MCP-1), vascular cell adhesion molecule 1 (VCAM-1), and intercellular adhesion molecule 1 (ICAM-1) [198]. In human vascular cells, resistin increased reactive oxygen species (ROS) production and impaired insulin Akt/eNOS signaling, suggesting that ROS may involve in resistin-induced endoplasmic reticulum stress [199]. In vitro analyses revealed that resistin activated protein kinase C type ε (PKCε) via TLR4 in smooth muscle cells; PKCε may represent a molecular target for resistin-associated chronic atherosclerotic inflammation [197]. Furthermore, plasma resistin levels correlate with inflammation markers and the may be predictive of coronary calcification, an indicator of atherosclerosis [200, 201].

The resistin receptor remains unidentified, although a recent report has suggested that resistin may bind to the endotoxin receptor TLR-4 [202]. In human monocytes, the inflammatory actions of resistin were mediated by its binding to adenylyl cyclase-associated protein 1 (CAP1), and in liver regulates insulin resistance-related genes [203].

Leptin

Leptin takes part in inflammation, immune cells, obesity, and T2D. This peptide is one of the most important WAT-derived hormones; it is the product of the ob gene, and structurally and functionally it may be classified as a cytokine. Leptin has a wide range of biological functions including both innate and adaptive immunity [204, 205]. In combination with cytokines and other molecules, it acts on the central nervous system, partially regulating food behavior and energy balance. It has an effect on energy metabolism in other tissues such as the liver and muscle [206].

Leptin controls food intake by interacting with anorexigenic molecules in the hypothalamus. These molecules are produced by cells secreting proopiomelanocortin (POMC) and by neurons releasing cocaine- and amphetamine-regulated transcript (CART), orexigenic molecules such as neuropeptide Y (NPY), and agouti protein (AgRP) [207, 208]. Animal models fed with an HFD show hyperleptinemia that generates a blockade of hormone functions resulting in resistance toward leptin, higher food consumption, and obesity [209].

Leptin acts by binding to a receptor (Ob-R). The latter is a class I cytokine receptor encoded by the rather ubiquitous LEP-R gene. Leptin receptors have been also detected in hypothalamic regions such as the arcuate and both paraventricular and ventromedial nuclei. These regions regulate energy balance. In studies, CRISPR-mediated deletion of LEPR in AGRP neurons causes severe obesity and diabetes, faithfully replicating the phenotype of Lepr db/db mice. The human leptin LEP-R receptors are coded by at least six homologue genes producing several mRNA variants [210–212]. It is also expressed on most immune cells, including neutrophils, macrophages, and lymphocytes. In the hypothalamus, leptin binds to its receptor on the plasma membrane, thus triggering a phosphorylation cascade [205]. One important function of leptin in the hypothalamus is to regulate body weight.

Obesity animal models lacking leptin or its receptor develop obesity due to hyperphagia caused by abnormal leptin/leptin receptor signaling, and subsequently T2D-like manifestations appear. These effects are secondary to genetic mutations that do not reflect the disease's etiology in humans, as leptin or leptin receptor deficiency is nor relevant for T2D. For more details, see review [213].

During food intake, leptin expression is stimulated in the TA. Conversely it is decreased during fasting and diabetes. Leptin synthesis is positively regulated by insulin, glucocorticoids, and estrogens, whereas catecholamines (through their β3-adrenergic receptors), androgens, and long-chain fatty acids inhibit its synthesis [214, 215]. Insulin-stimulated leptin secretion by adipocytes and the consequent stimulation of lipolysis and fatty acid release insulin and acts through the activation of the transcription factors: sterol regulatory element binding protein 1 (SREBP1), CCAAT-enhancer binding protein-α (C/EBP-α), and specificity protein 1 (Sp1) [216].

Leptin and insulin are mutually regulated. Thus, leptin inhibits insulin production in pancreatic β-cells, whereas insulin stimulates leptin production by adipocytes. Leptin stimulates the secretion of IL-1β from monocytes, and high levels of this cytokine inhibit insulin secretion and trigger proapoptotic signaling in pancreatic β-cells. When resistance toward leptin occurs, as characterized by hyperleptinemia, the homeostatic balance between these hormones is disrupted. Consequently, insulin production is not affected by leptin, and this results in hyperinsulinemia and resistance to this hormone [217, 218].

In human and mice, blood leptin levels closely correlate with AT mass [219]. In addition to its central effects, leptin may modulate the immune response. This hormone affects both the innate and adaptive branches of the immune system. Regarding innate immunity, leptin modulates the activity of NK cells, macrophages, and neutrophils by enhancing their function and promoting the production of proinflammatory cytokines [220–223]. Regarding adaptive immunity, several in vitro and in vivo experiments demonstrate that leptin positively impacts T-cell proliferation and increases Th1 cyto-

kine production while suppressing that of Th2 [218, 224, 225]. In monocytes, leptin increases the expression and release of the IL-1Ra anti-inflammatory cytokine [226], and on the contrary, IL-1Ra decreases leptin expression at both mRNA and protein levels [227, 228]. In healthy individuals it preserves the balance between inflammatory markers. However, when resistance to leptin occurs, this cytokine has a proinflammatory effect, and the balance is shifted toward the chronic inflammatory state particular of T2D and obesity [229].

Leptin-deficient mice (ob/ob) and those lacking its receptor (db/db) are obese because of their increased food intake resulting from impaired satiety. Additionally, they exhibit an important decrease of functional immune cell populations, such as NK cells, dendritic cells, and Treg cells [229, 230]. T and B cells have been shown to increase LEP-R expression when activated. Moreover, when leptin is included in the cell culture media, it increased the survival of activated lymphocytes [231].

Macrophage and NK cell populations increase during the first weeks after feeding an HFD, specifically in VAT [232]. In vitro leptin stimulation resulted in a higher production of interferon-γ in NK cells, but long-term leptin stimulation had no significant influence on numbers of proliferating NK cells [233]. Furthermore, leptin promotes NK cell survival in bone marrow; it attenuates macrophage infiltration and inflammatory gene expression in AT, in spite of weight gain and adiposity. In addition, deficiency of NK cells prevented proinflammatory macrophages in VAT and decreased insulin sensitivity. However, leptin does not affect weight gain and macrophage infiltration in this tissue. Different background strains, potential effects caused by gut microbiota, different body weight baselines, and differing fat percent in the diet may be the underlying cause of such contrasting results [17, 231, 232, 234]. These elements must be considered to further evaluate the role of leptin in macrophages.

Finally, all results support the concept that inflammation plays a role for T2D pathogenesis, and proinflammatory mediators produced by adipocytes and immune cells actively participate in this phenomenon.

IL-1Ra

The IL-1Ra cytokine is a natural IL-1β inhibitor. The expression and release of the former are induced by the latter, so this cytokine is usually controlled by its antagonist. Several cell types and tissues throughout the body express IL-1Ra; thus its high levels are probably needed in order to suppress the deleterious effects generated by the potent proinflammatory activity of IL-1β. When IL-1Ra competitively binds to the IL-1 receptor, IL-1β binding is blocked, and the conveying of proinflammatory signals from its receptor is hampered. Some evidences suggest that anti-inflammatory IL-1Ra counteracts the inflammatory effects mediated by IL-1β, and it preserves cell function in both types of diabetes [235].

High levels of circulating IL-1Ra are correlated with T2D incidence, but is decreased in islets from patients T2D. In a nested case-controlled study, those subjects who developed T2D during the 11.5-year follow-up period displayed higher IL-1Ra levels when compared to individuals who remained diabetes-free. The authors hypothesized that individuals with high risk of T2D are characterized by the presence of an early compensatory, anti-inflammatory response preceding the full development of the disease [138, 236]. The correlation between IL-1Ra levels and risk of T2D was also observed in subjects with metabolic syndrome in both cohorts. After adjustment for multiple confounders, IL-1Ra was significantly associated with metabolic syndrome (MetS) to T2D progression in males from both cohorts and in females from the FINRISK 97 cohort only. IL-1Ra displayed a significant correlation with risk of T2D in both cohorts when the data obtained from males and females was pooled [237, 238].

IL-1Ra improved β-cell function and glycemic control in patients with T2D; these effects were shown after treatment with anakinra, a recombinant of IL-1Ra. The positive effects of IL-1Ra were also observed on Goto Kakizaki (GK) rats (a spontaneous, no obese T2D model) and mice, as treatment with exogenous IL-1Ra protected them from increased proinflammatory cytokine expression in islets (IL-1β, IL-6, and TNF-α), chemokine expression, and macrophage infiltration in islets, and they also exhibited improved insulin processing. Treatment with IL-1Ra is not linked to body weight changes, either in patients or in animal models. Deletion of IL-1Ra in β-cells in mice triggered impaired insulin secretion, reduced β-cell proliferation, and decreased expression of islet proliferation genes, along with impaired glucose tolerance. Also, exenatide, a drug that increases IL-1Ra, protects, maintains, and stimulates β-cell function in humans [239–242].

Thus, when the IL-1β activity is blocked during T2D, both pancreatic β-cell function and insulin resistance are protected from the direct toxic effects caused by this cytokine and/or by antagonizing its inflammatory response [240, 241]. Therefore, IL-1Ra could be a new therapeutic agent to treat T2D.

IL-4

IL-4 is an anti-inflammatory cytokine secreted by Th2 lymphocytes, basophils, and mast cells. It has pleiotropic functions as it promotes the Th1/Th2 balance and

plays a major role in polarizing anti-inflammatory macrophage (M2), B-cell proliferation, and immune responses by regulating the proinflammatory mediators (IL-1β, TNF-α, and IL-6) produced by macrophages. IL-4 is secreted by AT and hepatocytes and then is able to modulate the local immune response and insulin sensitivity [243–245].

IL-4 may regulate insulin sensitivity, glucose tolerance, and lipid metabolism, and it could be involved in diabetic susceptibility and its complications. Leptin-deficient and leptin-resistant mice under high-fat diet (HFD) showed lower levels of circulating IL-4. The administration of IL-4 (8 weeks) improved metabolic dysfunctions. Also, the browning of white adipocytes by IL-4 was found in epididymal white adipose tissues and 3T3-L1 preadipocytes [246].

On the other hand, Fas-mutant mice exhibit leaner phenotype compared to wild type; under HFD they increased IL-4 and IL-10 levels, the promotion of thermogenic protein activity, and browning in their adipose tissues; then these mice are resistant to HFD-induced obesity [247].

Insulin sensitivity and glucose tolerance were improved in mice overexpressing IL-4; triglyceride accumulation in fat tissues was also inhibited, leading to decreased weight gain and fat mass [248]. Furthermore, 3T3-L1 adipocytes under culture conditions to induce insulin resistance were further cultured with IL-4, and they showed improved insulin sensitivity, but neither upregulated the expression of key adipogenesis markers (GLUT4 and PPARγ) and non-lipid accumulation [249]. Contrary, adipocytes isolated from rats and after incubation with IL-4 showed stimulated lipogenesis and inhibited both lipolysis and the expression of proinflammatory adipokines and also decreased adiponectin expression. Additionally, there is a correlation between IL-4/IL-4 receptor (R) genotypes and T2D and also between IL-4 genotypes and high-density lipoprotein-cholesterol (HDL-C) [250, 251]. This data reveals the previously overlooked roles of IL-4 in metabolism.

IL-10

IL-10 possesses multiple anti-inflammatory properties, including macrophage and T-cell inactivation, and it has a protective effect against atherogenesis. Adiponectin displays anti-atherogenic effects, partially by inducing IL-10 expression in human macrophages [252, 253].

Initially IL-10 was described as a product from Th2 cells that inhibits Th1 cell function. Currently, it has been identified that IL-10 is produced by most lymphocyte populations and the cells of the innate immune system, such as the antigen-presenting cells (DCs and macrophages), B cells, monocytes, and granulocytes affecting most hematopoietic cell types [252, 254–256].

In lean adipose tissue, iNKT cells and Tregs are abundant and they produce IL-10. During the adipose expansion occurring in obesity, iNKT cells and Treg populations are depleted, thus resulting in less IL-10 and a more inflammatory environment. This correlates with a proinflammatory macrophage accumulation. The decrease of iNKT and Tregs cells in obese AT contributes to local and systemic inflammation and eventually to T2D [257, 258].

IL-10 may protect against diabetes. In this regard, it was demonstrated that IL-10 overexpression in mice skeletal muscle prevented macrophage infiltration into the AT caused by a HFD. Subsequently, IL-10 restricted the expression of proinflammatory cytokines, and it promoted insulin sensitivity regarding control mice [259, 260]. The data obtained from humans attempting to correlate IL-10 and T2D are limited to a few cross-sectional studies. In a study conducted on 85-year-old subjects, it was observed that an elevated capacity of IL-10 production in whole blood was correlated with lower HbA1c levels and lower T2D prevalence [261]. Additionally, serum IL-10 inversely correlated with BMI and body fat, whereas a positive correlation was observed with insulin sensitivity when a euglycemic-hyperinsulinemic clamp was performed on subjects with impaired glucose tolerance or T2D, and also in mice, it was observed that IL-10 ameliorated hyperglycemia and insulin resistance [262, 263].

In a cohort of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), baseline blood IL-10 levels were positively correlated with the CRP and IL-6 proinflammatory mediators. During the follow-up period, IL-10 levels were increased, and they were associated with higher risk of cardiovascular events (death from coronary heart disease, myocardial infarction, and stroke) [264].

T2D patients showed increased numbers of circulating IL-10- and IL-17-producing CD3+ T cells when compared to controls, although there was no difference regarding the frequency of lymphocyte subsets. The authors suggest that these cytokines are involved on the immune pathology of this disease [265]. IL-10 is an interesting cytokine because of its potent anti-inflammatory effects. However, the reported data are contradictory, and currently it is not clear whether elevated circulating IL-10 levels are effective to negatively regulate proinflammatory reactivity and to confer protection against T2D or whether increased IL-10 levels are merely indicative of proinflammatory processes without providing a metabolic benefit.

Adiponectin

Adiponectin is highly expressed by adipocytes displaying potent anti-inflammatory properties. The ADIPOQ gene codes for adiponectin. This protein possesses a collagen-like domain N-terminal and a complement factor C1q-like globular domain C-terminal. It is highly expressed during adipocyte differentiation, and it is one of the main products secreted by adipocytes. In the bloodstream, it seems to occur as several isoforms: as a low-molecular-weight (LMW) trimer, as a medium-molecular-weight (MMW) hexamer (trimer-dimer), and as a high-molecular-weight multimeric (HMW) isoform [266].

Many studies have revealed that plasma adiponectin levels are significantly decreased in obesity, IR, and T2D, being a key component for the interplay between adiposity, IR, and inflammation. Adiponectin improves whole body insulin sensitivity, and its decreased levels occurring in obese rodents and humans are caused by the presence of proinflammatory factors such as TNF-α, IL-6, ROS, and hypoxia, as they suppress adiponectin expression in adipocytes [267–269]. Conversely, PPAR-γ antagonists stimulate this expression [270]. Independently, a meta-analysis study showed that increased risk of T2D was strongly associated with low adiponectin levels and high of inflammatory cytokine levels (TNF-α, IL-1β, IL-6, IL-18, CRP) [271].

Several studies described a significant negative correlation between adiponectin and obesity parameters. Serum adiponectin levels decrease when MetS components increase [272–274]. Additionally, urinary excretion of HMW-adiponectin is an independent predictor of kidney disease progression in T2D patients affected by early kidney disease, and serum adiponectin level can be a good predictor of diabetic nephropathy in patients with T2D [275–277].

Adiponectin beneficial effects on lipid and glucose homeostasis are caused by multiple mechanisms, mainly by ceramidase activity and adenosine monophosphate-dependent kinase (AMPK)/sirtuin 1 (SIRT1)-dependent activation of the PPAR cofactor 1α (PGC-1α) [278, 279]. In obesity models, fatty acid oxidation and glucose uptake in skeletal muscle and AT are stimulated by adiponectin, and it was shown that they are dependent on AMPK signaling. Adiponectin is also involved in hepatic glucose outsuppression mediated by AMPK activation [280, 281].

Obesity is correlated with increased cardiovascular risk, especially when it is concomitant with T2D. Patients with coronary artery disease (CAD) significantly showed reduced adiponectin levels when compared to controls with matching ages and body mass indexes [282–284]. It was also correlated with a low risk of myocardial infarction [285].

In addition to its antidiabetic functions, adiponectin also suppresses atherosclerosis, fatty liver diseases, and liver fibrosis [286, 287]. Adiponectin administration blocked the effect of proinflammatory agents, e.g., TNF-α and IL-6, and it directly improved endothelial dysfunction by increasing the production of nitric oxide [288].

Adiponectin acts as an immunomodulator; it promotes the differentiation of anti-inflammatory M2 macrophages [289, 290]. This adipokine also modulates T-cell activation and the inflammatory function of NK cells. Adiponectin receptors are upregulated on the surface of human T cells after an antigen-mediated stimulation, and they mediate apoptosis of antigen-specific T cells, subsequently suppressing T-cell expansion [291]. Furthermore, adiponectin suppresses TLR-mediated IFN-γ production in NK cells without affecting cytotoxicity [292]. Adiponectin inhibits LPS-induced TNF-α production in macrophages by inhibiting NF-κB activation and by stimulating anti-inflammatory IL-10 secretion [293, 294]. Therefore, adiponectin may contribute to this role by reducing inflammation within AT.

Two adiponectin receptors have been identified: AdipoR1 and AdipoR2. They possess seven transmembrane domains, although they differ structurally and functionally. The liver expresses AdipoR2, whereas the skeletal muscle contains AdipoR1 and AdipoR2. The biological effects caused by these receptors depend not only on adiponectin blood levels but also on tissue specificity. By interacting with its receptors, ADIPO R1/2, adiponectin activates AMPK to enhance fatty acid oxidation and glucose uptake in muscle and to suppress gluconeogenesis in the liver [295]. Moreover, adiponectin regulates energy expenditure by activating AMPK in the hypothalamus, where AdipoR1 and AdipoR2 co-localize with the leptin receptor, ObR [296]. It has been previously demonstrated that adiponectin stimulates appetite and decreased energy expenditure. These effects were eliminated following the ablation of AdipoR1 small interfering RNA (siRNA) or AMPK signaling (AMPK dominant negative) [297, 298].

Dysregulation of immune cells and released molecules from them may participate in the development of inflammation associated with metabolic diseases (Fig. 12.1). In an effort to revert these deleterious effects, the loss of weight, among several strategies, can help to avoid inflammation, pancreatic β-cell dysfunctions, insulin resistance, and then final steps to drive to T2D and other metabolic alterations (Fig. 12.2).

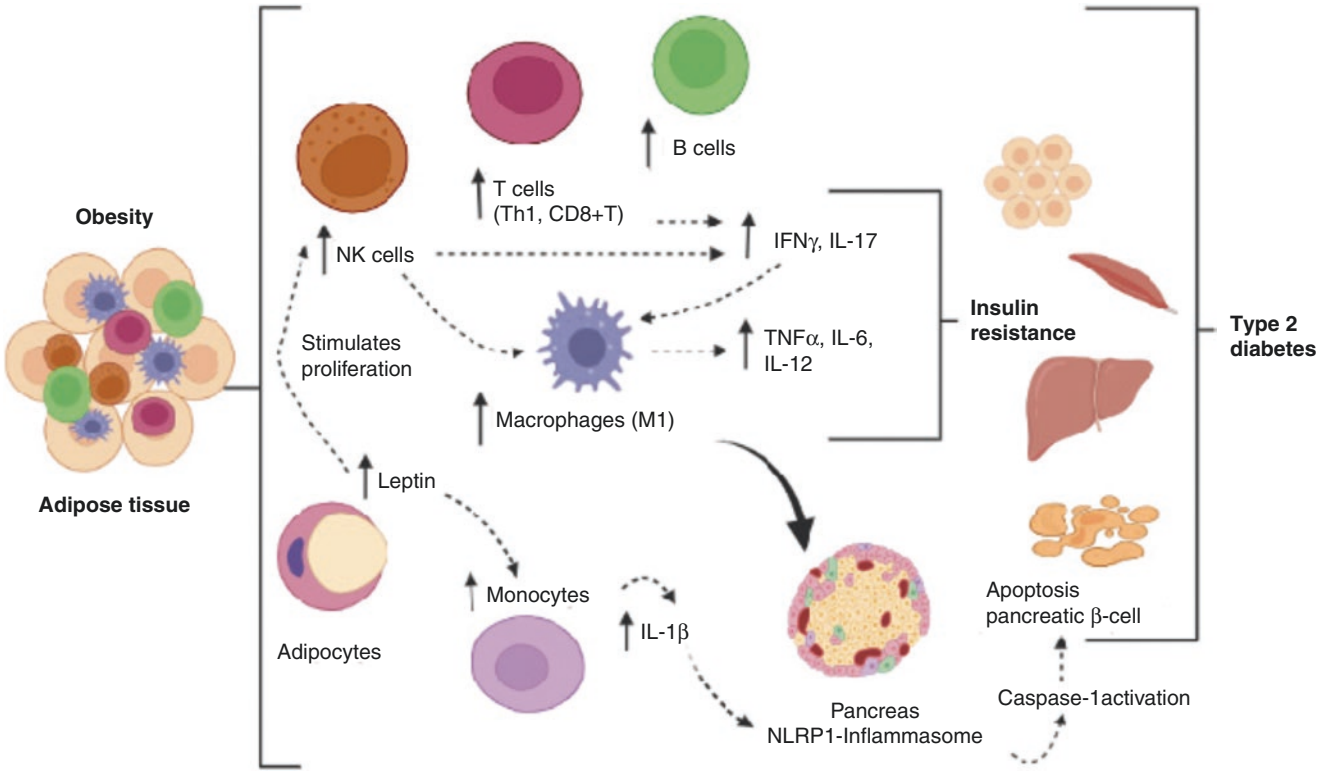

Fig. 12.1 Cells and molecules of the immune system may mediate insulin resistance associated with obesity and T2D. NK, T, B cells, monocytes, and other cells produce different cytokines (such as INF-γ, IL-17), which promote macrophage polarization to M1 phenotype, generating IL-6, IL-12, and TNF-α; these cytokines support an inflammatory milieu and insulin resistance. Furthermore, leptin, an adipokine increased in obesity, stimulates cells proliferation, such as NK cells, and also increases IL-1β secretion (from monocytes); this cytokine together with macrophages infiltration mediates β-cell dysfunction. All of these alterations contribute to T2D development. (The drawing was designed by Dr. A. Fortis)

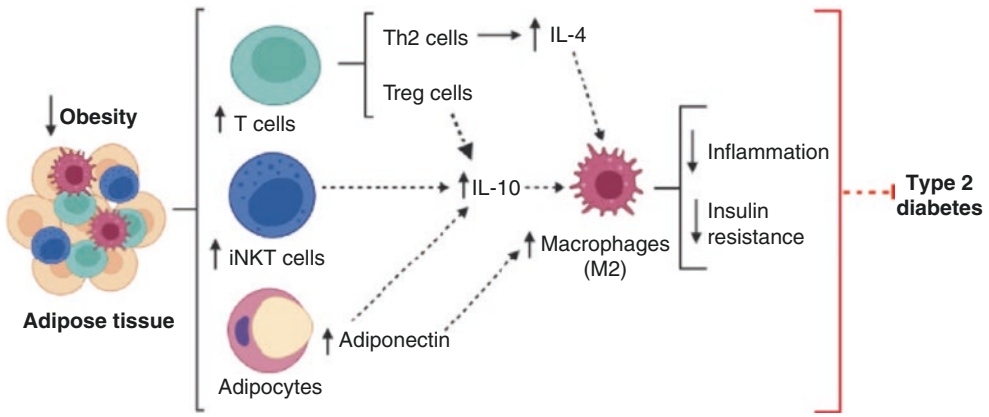

Fig. 12.2 The effect of reduction of obesity on immune cell functions. After weight loss, among other alternatives, the accounts of T cells (Th2 and Treg) and iNK cells increase, and IL-10 and IL-4, the cytokines generated by these cells, also increase. An increase in adiponectin levels (excreted by adipocytes) and macrophages polarization to M2 (anti-inflammatory phenotype) reduces inflammation, restorings insulin sensitivity and prevents T2D progression. (The drawing was designed by Dr. A. Fortis)

Perspectives onT2D Immunotherapy

The use of several anti-inflammatory methods has been implemented on obese subjects with IR. Based on this, salsalate (a salicylate analogue) has been shown to improve insulin sensitivity [299, 300]. The thiazolidinediones antidiabetics (e.g., rosiglitazone, pioglitazone, and lobeglitazone) induced a decrease of adipose tissue macrophage populations [301], and rosiglitazone increased adiponectin, ameliorates hepatic and systemic insulin resistance, hepatic inflammation, and fatty liver in rats [302]. Pioglitazone

reduced liver fibrosis and increased insulin sensitivity in patients with T2D [303]. Rosiglitazone in polymeric particles provide an efficient and selective delivery of the drug on specific place; it is a new strategy for therapeutic effects of TZDs reducing their secondary effects [304].

In patients with T2D, after a 12-week treatment with trelagliptin (an oral dipeptidyl peptidase (DPP)-4 inhibitor), serum adiponectin levels significantly increased [305]. Anti-TNF antibodies were proved to decrease blood glucose in obese subjects [3, 306]. Anti-IL-1β monoclonal antibody therapy improved glycemic condition and β-cell insulin secretion [307, 308].

Inflammation, improved insulin sensitivity, and normalized glucose tolerance were observed on obese mice fed with a HFD supplemented with *ω*-3 fatty acids [309]. Dietary supplementation with monounsaturated and *n*-3 polyunsaturated fatty acids showed a significant improvement in several functions such as chemotaxis, phagocytosis, digestion capacity, natural killer activity, and lymphoproliferation in response to mitogens [310]. In human studies, a supplementation with fish oil yielded mixed results regarding metabolic end points. A limitation of some of these studies has been the lack of discrimination between fatty and lean fish [311, 312].

IL-1β, the main macrophage-derived cytokine, increases in T2D obese subjects, and it enhances IL-17 and IL-22 release by AT CD4+ T cells. IL-22 stimulated pro-IL-1β transcription leading to enhanced IL-1β production by human VAT macrophages. Early clinical data describe promising effects caused by blocking IL-17 in several autoimmune diseases. An immunotherapy has been proposed by using an anti-IL-1β and anti-IL-22 antibody mixture in order to improve inflammation in human obesity-linked T2D [313].

Concluding Remarks

- Obesity, through adipose tissue expansion may contribute to the development of insulin resistance and type 2 diabetes.
- Adipose tissue is considered an important immunologically active organ and is constituted by adipocytes and immunological cells as macrophages, eosinophils, lymphocytes, etc.
- Immune cells participate on inflammatory processes, and they are the most represented cell types within adipose tissue.
- IL-1β, TNF-α, IL-6, and other cytokines expressed in immune cells and in adipocytes are promoters of inflammation.
- Insulin signaling is altered by proinflammatory cytokines and adipokines and they are important key targets to control or delay the T2D advance.

Multiple-Choice Questions

1. Inflammation associated with type 2 diabetes and obesity is mainly generated in this tissue or organ
   (a) Hearth
   (b) Kidney
   (c) **Adipose**
   (d) Muscle
   (e) Brain

   Answer: Inflammatory molecules are derived mainly on adipocytes and immune cells that constitute the adipose tissue.
2. Immune cells involved in diabetes
   (a) Myocytes
   (b) Cardiomyocytes
   (c) Astrocytes
   (d) **Lymphocytes**
   (e) Hepatocytes

   Answer: In obesity-associated diabetes, the number of lymphocytes increases.
3. Proinflammatory markers occurring in inflamed tissue
   (a) Glucose and sucrose
   (b) **Gamma interferon and interleukins**
   (c) Phospholipids and HDL
   (d) Leucine and proline
   (e) Insulin and glucagon

   Answer: Here, only interferon and interleukins are markers associated with inflammation.
4. Change that TNF-α undergoes between the lean and obese status
   (a) Inhibition
   (b) **Activation**
   (c) Inflammation
   (d) Polarization
   (e) Suppression

   Answer: TNF-α is activated during obesity and participates on insulin resistance development.
5. Effect caused by adiponectin on the arteries
   (a) **Antiatherogenic**
   (b) Pro-inflammatory
   (c) Insulin receptor-serine phosphorylation
   (d) Adipocyte dysfunction
   (e) Insulin deficiency

   Answer: Adiponectin is considered antiatherogenic due its effects on endothelial function by inhibition of ROS production and on monocyte adhesion.
6. Functions of mast cells
   (a) Secrete anti-inflammatory cytokines
   (b) Protect tissues from inflammation
   (c) **Secrete granules rich in histamine and serine proteases**
   (d) Express adiponectin mRNA
   (e) Protect from weight gain

Answer: Mast cells secrete granules rich in in histamine, serine proteases, and cytokines as a defense mechanism.

7. This effect has been demonstrated during development of type 2 diabetes.
   (a) Inhibition of adipocytes accumulation
   (b) **Macrophage recruitment in adipose tissue**
   (c) Decreased adiponectin expression in adipocytes
   (d) Increased serum IL-R1a
   (e) Inhibition of TNF-α activity

   Answer: There is a significant increase in the number of macrophages on adipose tissue from subjects with type 2 diabetes, which contributes to inflammatory process.
8. Invariant NKT (iNKT) cells
   (a) **Innate immune cells activated by lipids**
   (b) Cells that express INF gamma
   (c) The level of these cells increase in obesity
   (d) These cells produce high amount of IL-10
   (e) These cells are suppressed during obesity outset

   Answer: iNKT cells are innate lipid sensors, and their activation, using their prototypic ligand α-galactosylceramide.
9. It is a mouse macrophage marker.
   (a) CD28
   (b) CD40
   (c) **F4/80+**
   (d) CD4+
   (e) Th2

   Answer: F4/80+ are molecules found only on macrophage surface.
10. Regulation of this subtype of T cell is considered a novel target for treat type 2 diabetes
    (a) B cells
    (b) Th1
    (c) Th2
    (d) **Treg**
    (e) Th17
    (f) Mast cells

    Answer: Regulatory T cells (Tregs) are essential negative regulators of inflammation.

Glossary

Adipokine A cytokine or hormone that is secreted by adipose tissue

Chemokines Are signaling proteins secreted by cells, whose main function is to act as a chemoattractant to guide the migration of near cells. They are implicated in various diseases, such as cancer, autoimmune disorders, and diabetes

Cytokine Small proteins secreted and released by cells, they have a specific effect on the interactions and communications between cells

Diet-induced obesity (DIO) Obesity mouse model induced by high-fat diet

FA A carboxylic acid with aliphatic chains of 4–28 carbons, which can be esterified with glycerol to form triacylglycerols, the main stored form of lipids

HFD High-fat diet

IgG, IgM Are members of immunoglobulin (Ig) superfamily, they are ubiquitously present in several cells and tissues of vertebrates and share structural homology with cell adhesion molecules and some cytokines

Innate immune cells Are white blood cells that mediate innate immunity and include basophils, dendritic cells, eosinophils, mast cells, monocytes, macrophages, neutrophils, and natural killer cells

Mitogen-Activated Protein Kinase (MAPK) A mammalian Ser/Thr protein kinase

NF-κB Nuclear factor-κB is a ubiquitous transcription factor involved in the control of processes, such as immune and inflammatory responses, developmental, cellular growth, and apoptosis. The NF-κB pathway has been considered as proinflammatory signaling pathway, based on the role of NF-κB in the expression of proinflammatory genes including cytokines, chemokines, and adhesion molecules

Omental adipose tissue The fat depot found within the peritoneum, in close association with stomach and other internal organs

PPAR-γ Peroxisome proliferator-activated receptor gamma is an essential transcription regulator of the adipocyte differentiation and is required for mature adipocyte function

Salicylates A group of derivatives of salicylic acid, including aspirin and acetylsalicylic acid, which are widely used as analgesics, and anti-inflammatory medicaments

Thiazolinediones Antidiabetic drugs used therapeutically, which are known to be high-affinity ligand activators of PPARs

White adipose tissue (WAT) The predominant fat storage tissue in animals, consisting mostly of adipocytes but also other cell types as mast cells and macrophages

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[1]In the following references, you can find additional information about alterations of immune cells from adipose tissue during the development of type 2 diabetes, that are treated in the present chapter.

Dysfunction and Death of Pancreatic Beta-Cells in Type 2 Diabetes

13

Clara Ortega Camarillo

Abbreviations

AGE	Advanced glycation end products
AIF	Apoptosis inducing factor
Apaf-1	Apoptotic protease-activating factor 1
ATF6	Activating transcription factor 6
ATM	ATM serine/threonine kinase protein
Bak	Bcl-2 homologous antagonist killer
Bax	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma 2
Bcl-xl	B-cell lymphoma-extra large
BH (1–4)	Bcl-2 homology domains
Bok	Bcl-2 related ovarian killer
Caspasa	Cysteine-aspartic proteases, cysteine aspartases
CHOP	C/EBP homologous protein
ChREBP	Carbohydrate response element-binding protein
Drp1	Dynamin-related protein 1
ΔΨm	Mitochondrial membrane potential
eif2α	Eukaryotic translation initiation factor 2α
ER	Reticulum stress
ERE	Endoplasmic reticulum stress
EZH2	Enhancer of Zeste Homologue 2
FADD	FAS-associating death domain-containing protein
Fas	Death receptor
FFA	Free fatty acids
Fis1	Mitochondrial fission 1 protein
FOX A1/2	Forkhead box
G3P	Glyceraldehyde 3-phosphate
GADD34	Downstream growth arrest and DNA damage-inducible protein
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
GATA4/6	GATA-binding protein
GLUT	Glucose transporter
GSIS	Glucose-stimulated insulin secretion
H3K27me3	Histone H3 trimethyl K27
HNF1β	Hepatocyte nuclear factor
IAPP	Islet amyloid polypeptide
IFNγ	Interferon gamma
IGF1	Insulin-like growth factor 1
IL-1β	Interleukin 1 beta
iNOS	Nitric oxide synthases inducible
Ins	Insulin gene
INS1	Insulin secreting beta-cell-derived line
IRE1α	Inositol-requiring enzyme
IRS-2	Insulin receptor substrate
Isl	Islet
MafA	Musculo aponeurotic fibrosarcoma protein A
Mdm2	Murine double minute 2
Mff	Mitochondrial fission factor
Mfn	Mitofusin
Mouse *db/db*	Model of obesity, diabetes, and dyslipidemia with a mutation in leptin receptor
mTOR	Mammalian target of rapamycin
NAD^+	Nicotinamide adenine dinucleotide
NADH	Nicotinamide adenine dinucleotide reduced
NADPH oxi	Nicotinamide adenine dinucleotide phosphate-oxidase
NeuroD1	Neurogenic differentiation 1
NF-κB	Nuclear factor kappa B
Nkx	Homeobox protein
NLRP3	NACHT, LRR, and PYD domain-containing protein 3
NLRs	Nucleotide oligomerization domain (NOD)-like receptors
NO	Nitric oxide
NOD	Nucleotide oligomerization domain

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Notch	Transcription factor
•OH	Hydroxyl radical
8-OHdG	8-hydroxy-2′-deoxyguanosine
O–2	Superoxide anion
O-GlcNAc	O-linked β-N-acetylglucosamine
Opa1	Protein of mitocondrial internal membrane
P/CAF	P300/CBP-associated factor
p16	Cyclin-dependent kinase inhibitor 2A, multiple tumor suppressor 1
p21	Cyclin-dependent kinase inhibitor 1 or CDK-interacting protein 1
p27	Cyclin-dependent kinase inhibitor 1B
p300/CBP	E1A binding protein p300/CREB-binding protein
p38 MAPK	P38 mitogen-activated protein kinases
p53	Tumor protein p53
PARP	Poly ADP ribose polymerase
Pax4	Transcription factors paired box gene 4
Pdx1	Pancreatic and duodenal homeobox 1
PERK	Protein kinase-like ER kinase
PI3k	Phosphatidylinositol-3-kinases
PKC	Protein kinase C
PP-1	Protein phosphatase 1
Ptf1α	Pancreas transcription factor 1α
RAMP1	Receptor activity-modifying protein 1
Rfx 6	Regulatory factor x
RING-finger	Really interesting new gene
RINm5F	Rat insulinoma cells
ROS	Reactive oxygen species
Sox9 SRY	Sex-determining region Y-box 9
SPT	Serine C-palmitoyltransferase
T2D	Type 2 diabetes
TLRs	Toll-like receptors
TNFRI	Tumor necrosis factor receptor type I
TNFα	Tumor necrosis factor alpha
TXNIP	Thioredoxin-interacting protein
UCP2	Uncoupling protein 2
UDP-GlcNAc	Uridine diphosphate N-acetylglucosamine
UPR	Unfolded protein response

Objectives

- To briefly describe the embryonic development of pancreatic β
- To analyze the universal literature on the mechanisms that underlie the loss of pancreatic β-cell mass
- To provide information on the regulation of p53 by hyperglycemia and its participation in the induction of pancreatic β-cell apoptosis

Introduction

Insulin produced and secreted by β-cells is responsible for blood glucose level regulation. The major stimulus for insulin secretion is glucose itself. When the latter is taken by β-cells in a process mediated by the glucose transporter 2 (GLUT 2), it enters the glycolytic pathway, the Krebs cycle, and oxidative phosphorylation, and it promotes the increase of the ATP/ADP ratio. Subsequently, this leads to the closure of the ATP-dependent potassium channels, to membrane depolarization and to Ca^{2+} influx through the voltage-dependent Ca^{2+} channels. An increase of cytosolic Ca^{2+} is the signal that triggers glucose-stimulated insulin secretion (GSIS). Alterations of insulin secretion and glycemia increases lead to the settlement of type 2 diabetes (T2D). Additionally, this disease depends on external factors such as diet, body weight, and genetic background that may delay or enhance all clinical sings of the disease. It is known that, in modern society, an increased carbohydrate intake and the lack of exercising lead to the development of obesity. This condition increases insulin demand in order to maintain normal glycemia; thus the ability of β-cells in order to fulfill the insulin requirements is critical to preserve glucose homeostasis. The initial response toward an increased insulin demand is adaptive **hyperplasia** and an increased synthesis of the hormone [1]. However, if **resistance to insulin** persists during extended time periods, β-cells become exhausted, and their mass decreases due to an increase of the apoptotic rate and consequently hyperglycemia appears [2]. This latter condition activates several metabolic pathways impairing β-cells, such as glucolipotoxicity, mitochondrial alterations, oxygen reactive species (ROS), oxidative and endoplasmic reticulum stresses (ERE), proinflammatory cytokines, deposition of amyloid polypeptide, and p53 translocation to mitochondria (Fig. 13.1). Recently, it has been proposed that p53 protein is a major apoptosis trigger in β-cells during hyperglycemia conditions [3, 4]. These events impair β-cells by hampering their proliferative ability

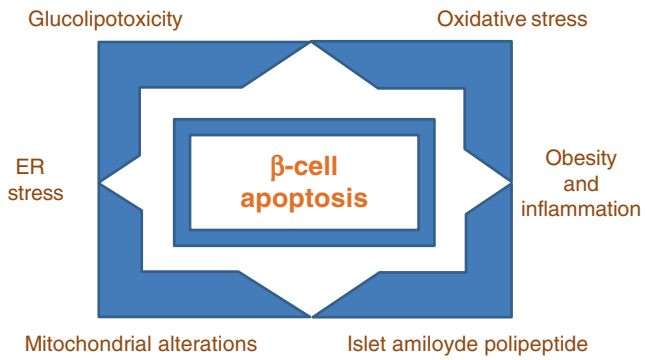

Fig. 13.1 Metabolic pathways by hyperglycemia induced β-cells death. *ER* endoplasmic reticulum

and also by decreasing insulin expression and secretion and promoting their death. Several of these alterations, either separate or combined, may be observed in T2D models; thus it is likely that β-cell loss in humans is linked to the activation of the aforementioned mechanisms and not to just one of them [5]. The contribution from each one of such mechanisms to the decrease of pancreatic β-cell amounts will be reviewed in this chapter.

The Origin of β-Cells

Embryonic Development and Differentiation

During embryonic development or even during the first postnatal days, β-cell may be generated by stem or progenitor cells within the pancreatic ducts, bone marrow, or even pancreatic islets. Islet genesis initiates on the week 12 of gestation in humans. In weeks 13–16, the early endocrine precursor cells on the duct's wall form cell aggregates and generate an early islet. In weeks 17–20, the connection between islets and duct is lost, and the islets are properly formed. At this stage, they contain only pancreatic polypeptide, somatostatin, and glucagon derived from immature precursor cells. In weeks 21–26, β-cells are located at the islet center [6].

Studies conducted on rodents have allowed the identification of the molecular mechanisms regulating pancreatic β-cell establishment and differentiation. In mouse, it begins on the E8.5 day of development, and it depends on several factors secreted by neighboring early gut cells and mainly from vessels. During pancreas development several transcription factors intervene, such as the pancreatic transcription factor (Ptf1a) and the pancreatic duodenal homeobox (Pdx1). Other factors such as SRY (sex-determining region Y)-box 9 (SOX9), forkhead box (FOX) A1/2, hepatocyte nuclear factor (HNF) 1β, and GATA4/6 have a critical participation during the establishment of the pancreatic progenitor cell pool. The development of endocrine progenitors requires Notch activation, whereas the formation of β-cells depend on Nkx 6.1, NeuroD1, the regulatory factor x (Rfx) 6, islet 1(Isl), Nkx2.2, and Pax4. The first hormone-producing cells are detected on E9.5, and their numbers increase by E13.5. At that time, the expression of β-cell-specific genes may be observed, such as GLUT 2 [7, 8].

Postnatal Development of the Pancreas

After birth, when feeding initiates, pancreatic mass increases due to the rapid expansion of the exocrine tissue. During the first 2 years of life, β-cell population keeps a 3–4% replication rate, and the pancreas reaches its maximum volume by 5–10 years old due to a decreased replication rate (0.05–0.1%) [9]. By the third decade of life, pancreatic mass is stabilized and constant until approximately 60 years of age. From that moment on, pancreas size begins to decrease [10] because an increase of cell proliferation inhibitors such as p16, p26, p27, and cyclin D3, whereas Pdx1 decreases. The latter is needed for β-cell differentiation [6]. In rodents, the β-cell population is established during the first 4 weeks of life. In rats, between postnatal days 3 and 24, a proliferation rate of 3% occurs, and during this period apoptosis also contributes to β-cell population curtailing. However, this stage is highly influenced by the prevailing nutrigenic environment [11].

In adults, during physiological conditions such as pregnancy or during adaptation toward weight increase, it is possible to observe an increase of β-cell replication rates [12]. It has been demonstrated that β-cell replication may be induced in rodents by providing a high-fat diet or a chronic glucose infusion [13]. Hyperglycemia also stimulates cell proliferation by activating glycolysis and by shortening the quiescence period of the cell cycle and also by promoting the G1-S transition through the activation of the ChREBP (carbohydrate response element-binding protein) transcription factor [5]. This confirms β-cell adaptive ability when facing a metabolic demand.

β-Cell Dysfunction and the Loss of Pancreatic B-Cell Mass

Chronic exposition of β-cells to high glucose levels impairs their functions, and it may induce dedifferentiation and even death and a decreased pancreatic β-cell mass (β-cell failure). The onset of β-cell progressive deterioration and loss of function occurs at an earlier stage, before TD2 symptoms even appear, which are evident due to decreased insulin synthesis and secretion [14]. Postmortem studies on human pancreas from patients with a clinical history of fasting glucose alterations demonstrated approximately a 50% decrease of β-cell mass caused by apoptosis [15]. Similarly, an increased glucose-induced insulin secretion was observed due to the remaining 50% [16]. However, the decreased β-cell mass is not only induced by an enhanced apoptosis as alterations of cell proliferation rates have also been documented. Additionally, during hyperglycemia conditions, other studies have reported that β-cell undergoes dedifferentiation or regression processes characterized by a decreased expression of the specific genes for these cells [17].

β-Cell Apoptosis

Apoptosis is a physiological mechanism for cell suppression that enables the elimination of some cells without affecting neighboring cells and without releasing the cell contents, unlike **necrosis** that is concomitant with an inflammatory reaction (Table 13.1). Apoptosis may be triggered through the activation of two major pathways: intrinsic or extrinsic. The latter is activated by death ligands that bind to cell surface receptors, thus transmitting death signals. Fas and TNFRI are the best described death receptors. They possess a cysteine-rich extracellular domain and a cytoplasmic death-domain. Fas ligand (FasL) binds to one of three Fas molecules, and it promotes receptor oligomerization and FADD (Fas-associated protein with death domain or Mort-1) interaction with the receptor's death domain. Subsequently, FADD binds to procaspase-8 leading to its activation. In turn, **caspase** 8 leads to the activation of other caspases, such as caspase-9. These are located within cytoplasm as inactive **proenzymes**, and they may be activated by other caspases, death receptors, or by **cytochrome c** [18] through its interaction with the apoptosis protease-activating factor-1 (Apaf-1) and procaspase 9, thus leading to **apoptosome** formation and the triggering of the caspase-activating cascade.

The extrinsic pathway initiates with the release of several proapoptotic factors, such as cytochrome c, from the mitochondrial intermembrane space toward cytosol. As mentioned above, this event lead caspase activation through the formation of the apoptosome, the activation of caspase 9, and the subsequent activation of executing caspases 3, 6, and 7 and with these the apoptosis proteolytic cascade. Mitochondria also release the apoptosis-induced factor (AIF), a **flavoprotein** that translocates to the nucleus where it triggers chromatin condensation and DNA fragmentation. Mitochondrial membrane potential ($\Delta\Psi_m$) alterations are also observed as well as respiratory chain uncoupling, all of them identified as early dysfunctions leading to cell death. Ceramides, oxidative agents, and pathologic increases of cytosolic Ca^{2+} may also induce the disruption of mitochondrial external membrane. Other proteins involved in permeating the mitochondrial membrane are those belonging to the Bcl-2 family. All of its members possess one to four preserved residues, known as the Bcl-2 homology domains (BHI to BH4). The apoptosis-inhibitor Bcl-2 and BcI-xl possess BH1 and BH2, whereas apoptosis-inducers such as Bax, Bak, and Bok display BH1, BH2, and BH3. There are some other proteins that only possess BH3 also known as death proteins. The Bcl-2 family members either promote or inhibit apoptosis in response to different stimuli such as lack of growth factors, Apaf-1 sequestration, and oxidative stress, among others [19].

Table 13.1 Apoptosis vs. necrosis

Apoptosis	Necrosis
Single cells	Cells group
Cell shrinkage	Cell swelling
Lysosomal enzymes are not involved	Involvement of lysosomal enzymes
Oligonucleosomal nucleus fragmentation	Complete nucleus dissolution
Apoptotic bodies	Cell disintegration
Phagocytosis by adjacent cells	Intracellular content release

At physiologic level, apoptosis is crucial for pancreas remodeling in newborns [20]. In adults, β-cell mass may increase and subsequently return to their normal size during some physiologic situations such as pregnancy and depending on the organism requirements. In other conditions as obesity and resistance to insulin, it has been proposed that β-cell hyperplasia may be reverted by body weight decreases and the increase of the apoptosis rate [21].

Whereas glucose-mediated stimulation is essential for physiologic maintenance of β-cells, chronic hyperglycemia induces severe damage to these cells, and it creates a vicious cycle contributing to the progressive loss of functional β-cell mass. Chronic hyperglycemia decreases β-cell sensibility toward glucose and induces exhaustion and toxicity. Desensitizing is a reversible protective mechanism facing a steady demand for insulin. When glycemia levels are restored and stimulation ceases, β-cells may regain their sensibility toward glucose [22]. Conversely, if hyperglycemia persists, β-cells become exhausted, thus implicating the loss of insulin granules and that of two transcription factors regulating insulin expression: the musculoaponeurotic fibrosarcoma protein A (MafA) and PDX-1. It is important to mention that these effects may also be restored when glycemia decreases [23, 24]. However, if resistance to insulin is persistent and glycemia increases, an overstimulation of β-cells occurs, thereby altering their functions and mainly the mechanisms for insulin synthesis and secretion [3, 21, 25–27]. If hyperglycemia is not adequately controlled, persistent stimulation of β-cells may eventually lead to degranulation, exhaustion, and apoptosis. In vitro studies have shown that culturing insulin-producing cells (RINm5F) in the presence of high glucose levels, an increased ROS production is observed and it triggers apoptosis [3]. In these conditions, Bax oligomerization also increases along with cytochrome c release and caspase-3 activation [21], but the precise mechanisms involved in β-cell apoptosis have not been completely elucidated.

Glucolipotoxicity

Although, free fatty acids (FFA) in physiologic levels contribute to preserve glucose-induced insulin secretion (GSIS). Exposition toward high FFA levels for prolonged periods,

along with hyperglycemia, affects the expression of the *Ins* gene and induces resistance to insulin and also pancreatic β-cell dysfunction. FFA contribute to apoptosis triggering in β-cells through activation of protein kinase C (PKC, apoptosis mediator), increases in ceramide synthesis and Bcl-2 inhibition [28], and increased levels of the type 2 uncoupling protein (UCP2) [29], thus decreasing ATP production [30] and glucose-induced insulin secretion, besides contributing to both oxidative and endoplasmic reticulum stresses [31, 32]. It has been observed that unsaturated fatty acids (e.g., palmitic acid) are more toxic when compared to their monounsaturated counterparts (e.g., palmitoleic acid), as the latter may even exhibit a protective effect because they are rapidly esterified in order to form **triacylglycerols** [33]. However, it is currently accepted that FFA-induced damage depends on concentration, exposure time, and blood glucose levels [32, 34]. When these factors converge, fatty acids and glucose compete for metabolism through the glycolytic pathway. During hyperglycemia, oxidative phosphorylation becomes saturated with glycolytic products, thus promoting the formation of manoyl-CoA that inhibits the β-oxidation of fatty acids. This effect forces β-cells to divert fatty acids to other metabolic pathways in order to metabolize them; thereby it increases the production of esterified fatty acids such as **ceramides** [35]. Accumulation of the latter occurs from sphingomyelin cleavage and/or de novo ceramide synthesis by condensing serine and non-oxidized palmitoyl-CoA through the activity of serine-palmitoyl transferase (SPT) located in the mitochondria and endoplasmic reticulum. Ceramides affect mitochondrial membrane potential and permeability, and they represent a ROS production mechanism. They also enable the release of apoptosis induction factors such as cytochrome c and procaspases, thus leading to β-cell death [36]. Some experiments have demonstrated apoptosis induction mediated by ceramides after inhibiting their synthesis. In such conditions fatty acid-induced apoptosis also decreases [35]. Additionally, ceramides induce the activation of the NF-κB transcription factor that increases both inducible and non-inducible nitric oxide (NO) production. The interaction between NO and O^{-2} produces peroxynitrite, thus inducing DNA damage and the activation of poly (ADP-ribose) polymerase (PARP), a NAD^+-dependent enzyme [36]. Therefore, its over-activation decreases both, the NAD^+ pool and glycolytic rate, electron transport, and ATP synthesis. Besides negatively affecting insulin secretion, this situation may lead to pancreatic β-cell death [37].

Oxidative Stress

Whereas low ROS levels exert a beneficial effect on β-cells [11], their overproduction causes oxidative damage to proteins, lipids, and nucleic acids, and it induces oxidative stress. In hyperglycemia conditions, ROS are mainly generated by glucose auto-oxidation and also through an increased electron flow in mitochondrial respiratory chain [38]. Although, in recent years, it has been demonstrated an important participation of the NADH oxidase complex [3], as their components have been identified in rat pancreatic β-cells [39]. An increased mitochondrial pathway initially accelerates NADH production. The latter participates in the mitochondrial respiratory chain, and it represents the first step for superoxide anion ($O^{-}_{2}\cdot$) production that also generate other radicals such as hydrogen peroxide (H_2O_2) and the hydroxyl radical ($^{\circ}OH$), one of the most potent biomolecule oxidants. An increased $O^{-}_{2}\cdot$ inhibits glyceraldehyde 3-phosphate dehydrogenase (GAPDH) inducing accumulation of glyceraldehyde 3-phosphate (G3P) within the glycolytic pathway. This leads to the activation of ROS-producing pathways and to oxidative stress [40, 41] in the form of advanced glycation end-products (AGE), as their precursor (methylglyoxal) is generated from G3P. It also leads to PKC activation as glycerol (its activator) is also produced from G3P (Fig. 13.2) [42].

Alterations induced by oxidative stress range from synthesis modifications and insulin secretion, endoplasmic reticulum stress, and activation of the apoptotic intrinsic pathway [9]. ROS lead to activation mechanisms that reinforce β-cell death and their decreased cell mass. They also induce mitochondrial membrane potential alterations, thus modifying permeability and the release of proapoptotic proteins (cytochrome c, apoptosis-inducing factor, among others) and activating the apoptotic proteolytic cascade [3]. β-cell susceptibility toward the damage induced by free radicals and their low abundance of **antioxidant** mechanisms have been previously demonstrated [41]. Therefore, it is considered that oxidative stress is greatly responsible for pancreatic β-cell death after being exposed to hyperglycemia. The ROS-induced damage on β-cells have been quantified by the presence of 8-hydroxy-2-deoxiguanosine (8-OHdG) on subjects affected by T2D, in animal models [32] and in vitro on insulin-secreting cells [3, 43]. It has been demonstrated that H_2O_2 addition to rat and mouse β-cell cultures alters mitochondrial membrane potential; it decreases ATP levels as well as glucose-induced insulin secretion (GSIS) [44]. This effect is abolished when the expression of antioxidant enzymes is increased. GSIS decrease induced by ROS has been linked to GAPDH and glycolysis, and, as previously mentioned, it consequently decreases ATP levels.

In addition to direct damage induced on biomolecules, oxidative stress favors the activation of other pathways such as O-glycosylation, poly ADP-ribosylation, and *N*-acetylglucosamination. All of them may modify or inhibit the function of proteins. Approximately 2–3% of glucose entering β-cells is diverted to the hexosamine biosynthesis pathway in order to synthesize uridine diphosphate

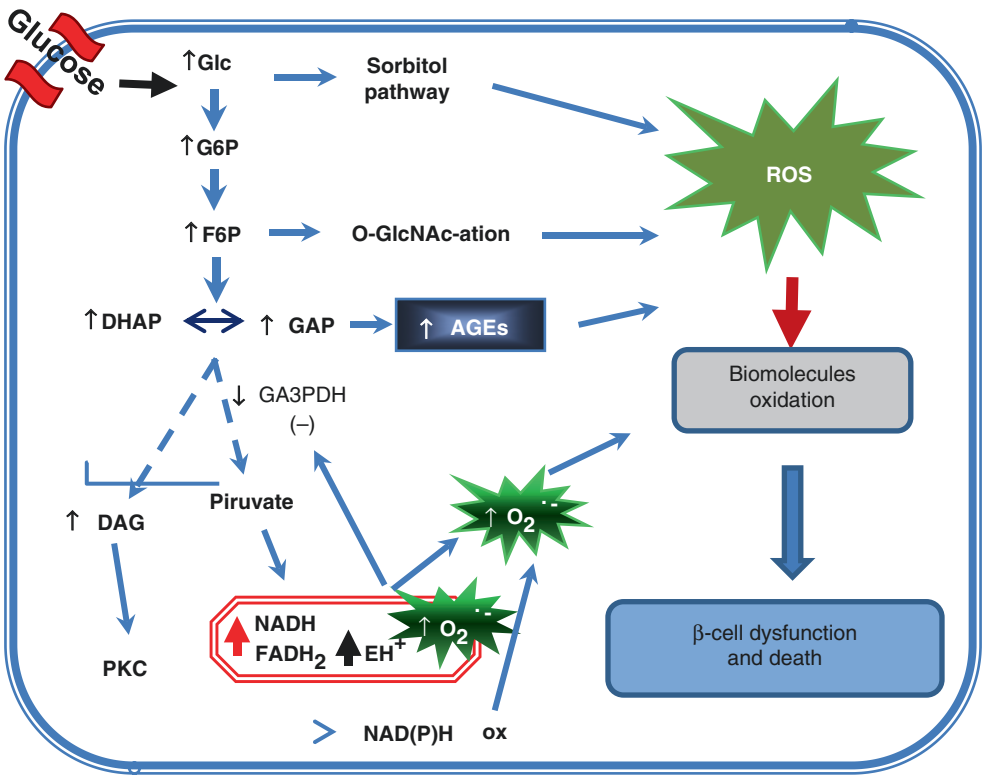

Fig. 13.2 Hyperglycemia induces ROS production and oxidative stress by increasing glycolysis and phosphorylation pathways. This situation induces biomolecule oxidation and β-cell exhaustion and death. *ROS* reactive oxygen species, *O-GlcNAc-ation* glucosaminylation, *AGES* advanced glycation end-products

N-acetylglucosamine (UDP-GlcNAc); thus O-GlcNAcylation regulates protein function depending on glucose availability. Among the proteins prone to modification by OGT are Pdx1, FoxO1, NeuroD1, IRS2, Akt, and p53; thus it regulates glucotoxicity and β-cell apoptosis [11].

Mitochondrial Alterations

Mitochondrial physiology plays a very important role on the regulation of the insulin secretion mechanism. When exposed to hyperglycemia, β-cell mitochondria exhibit important functional and morphological changes that affect the ATP/ADP ration required for insulin release. ROS increased due to hyperglycemia modifies mitochondrial permeability and induce apoptosis. ROS oxidizes **cardiolipin**, a phospholipid responsible to preserve mitochondrial architecture and membrane potential maintenance, and it also provides support for proteins involved in mitochondrial bioenergetics. Through hydrophobic and electrostatic interactions, cardiolipin keeps cytochrome c attached to the inner membrane. During early apoptosis, ROS oxidize cardiolipin, and they disrupt its interaction with cytochrome c that become detached from inner membrane, and it is released to cytoplasm [45], where it participates for apoptosome formation in order to activate proapoptotic caspases (intrinsic pathway). Cardiolipin is also the target of the proapoptotic protein tBid that is activated by caspase-8 (extrinsic pathway). tBid promotes pore formation on the external membrane mediated by Bax and Bak [46]. Thus, cardiolipin is a central regulator to achieve the activation of both apoptotic pathways.

Mitochondrial integrity and abundance are also regulated by **fission** and fusion mechanisms. These processes, although opposite, are coordinated in order to preserve mitochondrial morphology, size, and abundance. Mitochondrial fusion is regulated by **mitofusins** 1 and 2 (Mfn1 and Mfn 2) as well as by the mitochondrial inner membrane protein (Opa1). Mitochondrial fusion allows the exchange and merging of the organelle's content, including membranes, genetic material, and other metabolites. It also contributes for mitochondrial function preservation in metabolic stress conditions and during glucolipotoxicity [47]. Conversely, mitochondrial fission is mediated by several proteins such as the transmembrane fission protein (Fis1), the membrane fission factor (Mff) on the external membrane, and the GTPase dynamin-related protein 1 (Drp1). Fission is essential in order to segregate damaged or dysfunctional mitochondria [48]. Alterations of mitochondrial dynamics balance mediated by the loss or gain of proteins regulating fusion or fission events impact on mitochondria structure (fragmentation) and their function as well as glucose-dependent insulin secretion [47].

In response to glucose, cell energy and mitochondrial membrane function are also regulated by **uncoupling proteins** (UCPs) located at their external membrane. UCPs are mitochondrial transporters on the inner membrane that regulate the coupling status of the respiratory chain as well as

ATP synthesis. Thus, they keep the necessary ATP/ADP needed for glucose-stimulated insulin secretion. They also contribute to the mitochondrial antioxidant defense by inducing physiologic uncoupling that accelerates metabolism and decreases ROS and oxidative stress [29]. Five uncoupling proteins have been identified in humans as important regulators of corporal weight gain, the energy balance, and T2D. The most important are UCP-2 and UCP-3 because of their participation for mitochondrial membrane potential maintenance and ATP production. UCP-2 protects β-cells against oxidative stress. INS-1 cells cultured in the presence of H_2O_2 increase UCP-2 expression as well as survival rate; they also decrease ROS and caspase activation—however, hyperglycemia and **hyperlipidemia** increase UCP2 activation; consequently they reduce ATP synthesis and insulin secretion. UCP-2 also promotes mitochondrial membrane potential alterations along with the consequent release of proapoptotic factors and β-cell dysfunction that may lead to apoptosis [49].

Endoplasmic Reticulum Stress

Oxidative and endoplasmic reticulum stress (ERS) are interlinked regarding β-cell dysfunction because of their direct effects on insulin biosynthesis and secretion [50]. The endoplasmic reticulum (ER) ensures the appropriate folding and processing of proteins that will be secreted, among them insulin, as well as the degradation of **misfolded proteins** or those exhibiting alterations. Thus, the organelle's overload leads to misfolded protein accumulation and ERS. The latter triggers the unfolded protein response (UPR) in order to restore ER homeostasis and to decrease protein synthesis. It also increases the expression of genes involved in protein folding and ER-linked protein degradation. UPR is mediated by proteins bound to the ER membrane: PERK (protein kinase-like ER kinase), IRE1α (inositol-requiring enzyme), and ATF6 (activating transcription factor 6) [51]. When stress occurs, PERK autophosphorylation induces eif2α (eukaryotic translation initiation factor 2α) phosphorylation, a factor that inhibits protein synthesis, whereas it promotes ATF-4 transcription. The latter positively regulates the expression of ERS target genes such as the C/EBP homologous protein (CHOP) and the downstream growth arrest and DNA damage-inducible protein (GADD34). These two proteins activate protein phosphatase-1 (PP-1) that in turn dephosphorylates eif2α, thereby restoring transcription. Acute exposition of β-cells to high glucose levels induces an intermediate UPR signaling characterized by IRE1α phosphorylation and activation as well as glucose-stimulated insulin secretion. However, excessive UPR stimulation induces β-cell death and diabetes. In patients displaying insulin resistance and in islets isolated from *ob/ob* mice, it has been demonstrated that a constant and steady demand for insulin represents ER constant stimulation, and it eventually leads to stress [51]. Additionally, the increase of FFA also induces ER stress as it affects protein processing and trafficking, Ca^{2+} regulation, and oxidative stress in mouse insulin-producing cells (INS1) and in human cell lines [52]. Palmitate activates the UPR response through phosphorylation of IRE1 and PERK as well as β-cell apoptosis mediated by caspase-12 and caspase-3 activation [53].

Obesity and Inflammation

Currently, obesity stands out as a risk factor to develop T2D. Nevertheless, if obesity actually causes diabetes, most obese individuals sooner or later would develop hyperglycemia and T2D. In spite of this, approximately 20% of all obese individuals are diabetic [54]. This suggests that obesity and resistance toward insulin are factors that increase the risk to develop diabetes, but they are not inductors. Thus, it has been proposed that, in obese individuals, hyperglycemia may be more related to β-cell-impaired function and decreased mass [55] and/or their inability to adapt themselves toward the new metabolic demand [56]. Even though some of these studies have demonstrated a decreased β-cell mass in obese humans affected by T2D (postmortem donors) and in those who displayed alterations of fasting glucose levels by 65 and 40%, respectively [12], in obese individuals not affected by T2D, β-cell mass and insulin secretion are increased by 50% in order to cope with resistance to insulin [57]. In obese rodents a physiologic-adaptive expansion of β-cells is observed due to increased generation, decreased death, and β-cell hypertrophy [58]. Through this adaptation, β-cells preserve normal glycemia until they become exhausted and eventually die, thus leading to T2D development. Cell expansion is a complex process involving the activation of several pathways that converge to regulate proliferation, survival, cell size, and insulin secretion. Apparently, proliferation and hypertrophy are most important during the β-cell expansion phase, whereas apoptosis may participate in the final phases, during β-cell failure caused by hyperglycemia. Some evidence shows that, in animals displaying resistance toward insulin, the IGF1/PI3k/Akt/mTOR pathway participates during β-cell adaptation induced by a high-fat diet. mTOR (mammalian target of rapamycin) mediates protein synthesis in response to nutrients and growth factors, and it stimulates the phosphorylation of some components of the protein synthesis machinery such as p70S6K (ribosomal S6 kinase protein) and 4E-BP (IF4E-binding protein). Akt also participates in cell cycle regulation by inducing phosphorylation and degradation of the cyclin-dependent kinase inhibitors such as p21 and p27. Apparently, the increased β-cell mass in obese individuals

may be a reversible event, similarly to pregnancy. Some studies have reported that insulin secretion decreases concomitantly with weight loss or caloric restriction, whereas sensibility toward insulin is regained as well as β-cell function. Furthermore, caloric restriction enhances mitochondrial biogenesis and respiratory efficiency; it decreases ROS production and promotes metabolic homeostasis [59].

Additionally, because of the FFA increase, obesity predetermines a chronic inflammation state in adipose tissue that is characterized by increased proinflammatory **adipokines** and cytokines. These attract B-cells, T-cells, and macrophages toward the pancreas and adipose tissue where they secrete even more proinflammatory cytokines and chemokines, thereby contributing to inflammatory reaction and to autoimmune elimination of β-cells. The presence of reactive T-cells in islets is observed in patients affected by T2D exhibiting severe β-cell lesions and low insulin secretion [60]. Obesity implies an increased amount of adipocytes and also of their fat content, a vascularization decrease, hypoxia, and cell necrosis. Signal molecules derived from cell elimination may bind to Toll-like receptors (TLRs) and to nucleotide-binding oligomerization domains (NOD) in order to induce a local or generalized immune response. The latter consists on the assembly of cytosolic protein complexes comprised by bound nucleotides, leucine-rich repeats sequences (NLRs), and caspase-1. Once active, they initiate IL-1β production [61]. Hyperglycemia increases the production of the NLRP3 **inflammasome**, whereas FFA activate TLR2 and TLR4, thus promoting macrophage recruitment and β-cell stress [60].

Plenty of evidence exists on the importance of proinflammatory cytokines (IL-1β, TNF-α, and interferon-γ (IFN-γ) to activate signaling cascades in β-cells, such as NF-κB, the mitogen-activated protein kinase (MAPK), and the Janus kinase/signal transducer and activator of transcription (JAK/STAT). β-cell elimination by the proinflammatory cytokines IL-1β, TNFα, and IFNγ begins by their binding to specific receptor in β-cells and to the endoplasmic reticulum [61]. The consequences of increased ROS were previously mentioned. Conversely, in the presence of cytokines, the 12/15-lipoxygenase (12/15-LO) induces the cleavage of arachidonic acid to produce highly reactive metabolic such as 12-hydroxyeicosatetraenoic that may induce oxidative stress and mitochondrial dysfunction [32]. It has been also demonstrated that thioredoxin-interacting protein (TXNIP) interacts with NLRP3 and contributes to IL-1β production induced by hyperglycemia [62]. The latter contributes to β-cell dysfunction and apoptosis in T2D. TNFα negatively regulates the insulin receptor substrate 2 (IRS-2) in β-cells by inducing its phosphorylation and modifying insulin signaling. In obesity leptin secretion by adipose tissue also predominates. Leptin inhibits glucose-induced insulin secretion in β-cell lines and normal mice [63], and it also contributes to intolerance toward glucose in diabetes.

B-Islet Amyloid Polypeptide (IAPP)

Amylin is synthesized by pancreatic islets, and it is secreted along with insulin. Amylin is comprised by 37 amino acids, although it may produce polypeptides and be accumulated in islets in response to stress. IAPP effects initiate after binding to its receptors. Only three of them are known. They contain the calcitonin receptor in their inner structure and one of the following three receptor activity-modifying proteins: RAMP1, RAMP2, or RAMP3. The accumulation of intracellular amylin has been linked to both oxidative and endoplasmic reticulum stresses. β-amyloid plates are a common feature in patients affected by T2D. During hyperglycemia/hyperlipidemia, IAPP synthesis also increases in β-cells along with proinsulin, and they reach enough levels in order to allow for oligomer formation [20]. They also stimulate IL-1β, islet inflammation, and β-cell apoptosis. IAPP-soluble peptides have been detected. They represent early intermediates for fibril formation, and they are also responsible for cell death. In peripheral tissues, IAPP modifies glucose metabolism [64]; it suppresses glucose uptake induced by insulin in muscle cells [65] and digestive secretion (gastric acid, pancreatic enzymes), and it delays gastric emptying. IAP administration to rats decreases food intake [66], but when an IAPP antagonist is provided, food intake increases as well as body weight [67].

β-Cell Apoptosis and p53

β-cell apoptotic death after being exposed to high glucose levels has been associated with p53 protein translocation toward mitochondria [3]. Furthermore, β-cell population recovery and the rescue form the diabetic phenotype was demonstrated in p53-knockout mice, thus highlighting the importance of this protein for diabetes establishment [4].

The p53 protein is a transcription factor engaged in DNA damage monitoring. Depending on the severity of the damage, p53 triggers apoptosis or arrests the cell cycle until the DNA-repairing mechanisms are activated. p53 activation occurs in response to several types of stress, mainly those damaging DNA, and this leads to its stabilization and accumulation in cells submitted to stress conditions. p53 is also involved in apoptosis triggering by interacting and forming

complexes with Bcl-2 and Bcl-XL through its DNA-binding domain, thus allowing Bax-Bax oligomerization and the release of cytochrome c [68].

Apoptosis onset induced by p53 at mitochondria level is associated with oxidative stress. In insulin-producing cells (RINm5F) cultured on glucose 30 mM, p53 translocation to mitochondria, cytochrome c release, and apoptosis were induced because of oxidative stress [3]. Taking this into account, it was proposed that glucose increase modifies intracellular p53 distribution, and it promotes its mitochondrial localization besides inducing p53 phosphorylation, impairing its degradation, and increasing its biologic activity [69]. The presence of p53 in mitochondria is correlated with a decreased Bcl-2/Bax ratio and a decreased mitochondrial membrane potential [3], p53 activation, and increases of p21, Bax, and apoptosis [70]. This emphasizes p53 participation during the decrease of β-cell mass induced by hyperglycemia.

Hyperglycemia regulates p53 stability and function by inducing posttranslational modifications such as phosphorylation, poly(ADP-ribosylation, and N-acetylglucosamination [71].

p53 Phosphorylation

Hyperglycemia promotes p53 mitochondrial localization and its phosphorylation at serine 392 (homologous to Ser289 in mouse). This correlates with a Bcl-2 decrease, Bax increase, and β-cell apoptosis. The inhibition of the p38 MAPK hampered p53 phosphorylation, and it curtailed β-cell apoptosis induced by hyperglycemia, thereby suggesting its participation during the decrease of pancreatic β-cell mass. As in mitochondria p53 is engaged in complex formation with other antiapoptotic and/or proapoptotic proteins, and as it triggers the mitochondrial permeation process, it is likely that its phosphorylation is a requirement that may enable its interaction with such proteins and to induce cell death. Additionally this process stimulates the interaction between p53 and the p300/CBP and P/CAF coactivators that promote its acetylation, thereby inhibiting its ubiquitination and degradation [72]. These results indicate the importance of p53 phosphorylation as one of the factors contributing to β-cell elimination as a consequence of hyperglycemia through mitochondria (Fig. 13.3). Hyperglycemia also leads to ATM activation in cytosol, which in turn phosphorylates p53 at serine15, thus avoiding its recognition by Mdm2, its ubiqui-

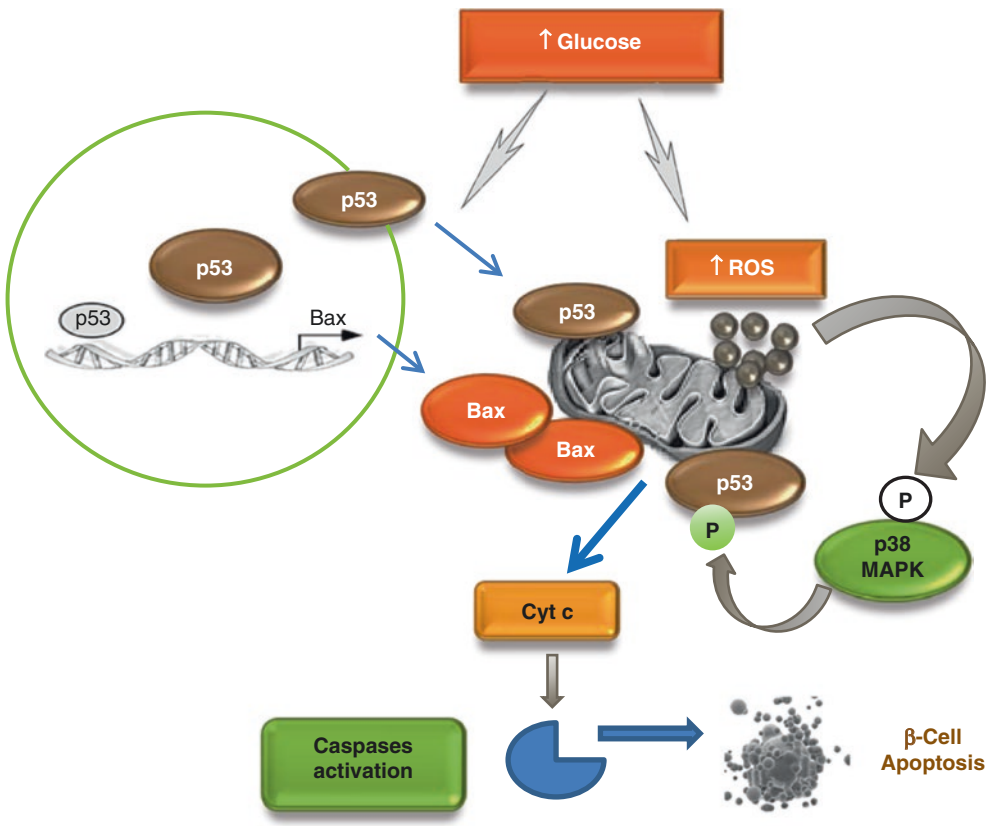

Fig. 13.3 Hyperglycemia promotes p53 translocation to mitochondria and its phosphorylation. p53 contributes to mitochondrial permeability, cytochrome c release, and β-cell apoptosis. *P* phosphorylation, *ROS* reactive oxygen species, *Cyt c* cytochrome c

tination, and nuclear degradation and also contributing to apoptosis triggering in response to hyperglycemia in β-cells [73].

p53 O-N-Acetylglucosamination

Hyperglycemia promotes N-acetylglucosamination (O-GlcNAc) of several proteins, including p53. This consists on the addition of a *N*-acetyl-glucosamine moiety in serine or threonine residues. O-GlcNAc is analogue to phosphorylation, and it regulates the stability, activity, or subcellular localization of target proteins. This modification depends on glucose availability, and it represents a cellular regulation mechanism according to nutritional environment. In a glucose-rich environment, the O-N-acetylglucosamination of p53 has been observed, and it is liked to its stability, and it prevents its degradation. O-GlcNAc in p53 at Ser149 enhances its stability by interfering with phosphorylation at Thr155, by overcoming its interaction with Mdm2 and its ubiquitination and its subsequent proteolysis. All of this results in higher p53 stability [74]. Thus, it has been proposed that O-GlcNAc stabilizes p53 and it may represent a signal for its translocation to mitochondria [73], where it may contribute to the release of proapoptotic factors [75].

p53 Poly(ADP-Ribosylation)

Another protein that becomes active when DNA suffers damage is poly(ADP-ribose) polymerase (PARP). This enzyme catalyzes the transfer of ADP-ribose units from NAD^+, an essential cofactor for ATP synthesis and redox potential balance, to the carboxylic residues glutamic and aspartic acids of several nuclear proteins. Poly(ADP-ribosylation) is important for DNA replication and repair, transcription, inflammatory response, and cell death mainly caused by genotoxic agents, infection, and stress. PARP fragmentation is concomitant with β-cell apoptosis triggering induced by hyperglycemia. These results are in agreement with previous reports showing that hyperglycemia triggers apoptosis in β-cells and pancreatic cell lines such as RINm5F. Poly(ADP-ribosylation) of p53 in the presence of high glucose levels is an early response that may contribute for protein stabilization and probably to its translocation to mitochondria as well as to the increased apoptotic rate of RINm5F cells caused by high glucose levels [75].

p53 Regulation by Mdm2

Cell survival depends in great extent on the balance between synthesis and degradation of p53. Among the mechanisms regulating p53, the expression and activation of Mdm2 (murine double minute 2) is of great importance. Mdm2 is an E3 ubiquitin ligase that binds p53, and it transfers **ubiquitin** to the latter residues, thereby enabling its recognition by **proteasome**s for targeted degradation. Depending on the amount of ubiquitin residues attached to p53, this protein will be degraded or exported to the cytosol. Mono- and/or poly-ubiquitination of p52 is defined by the concentration and activation status of Mdm2.

As previously mentioned, the interaction between p53 and Mdm2 depends on intracellular environment impacting on those posttranslational modifications displayed by these proteins. In the case of Mdm2, ubiquitination, **sumoylation**, and phosphorylation disrupt the formation of the p53-Mdm2 diene, and they stabilize p53 levels. It has been demonstrated that Mdm2 phosphorylation on Ser395 mediated by ATM decreases its ability to target p53 for degradation. Previously it was demonstrated that p53 phosphorylation by Akt participates in its regulation as it attenuated transactivation and increased p53 ubiquitination [76]. High glucose concentration decreases the expression of Mdm2 mRNA and its protein levels on both nucleus and cytosol [77]. Mdm2 expression is regulated by p53. Although we previously demonstrated its stabilization in presence of high glucose levels, this protein is not targeted toward the nucleus, but it translocates to other organelles such as mitochondria; thus it cannot stimulate Mdm2 expression. Additionally, DNA fragmentation induced by hyperglycemia also may affect the expression of Mdm2 mRNA [3].

The formation of the p53-Mdm2 complex increased in the presence of high glucose, although its ubiquitination was not observed. The latter demonstrates that glucose-increased levels induce Mdm2 activation in cytosol and its interaction with p53 is also promoted, whereas its ubiquitination is inhibited [73]. It is known that the E3 ubiquitin ligase activity of Mdm2 depends on other domains comprising this protein. The latter activity is located within the **RING finger domain** at the C-terminal. This region also contains the substrate lysine acceptor, and its main function is to label p53 for degradation. The central acid domain of Mdm2 binds to the RING finger domain, and it stimulates catalytic activity, thereby promoting ubiquitin release from the E3 enzyme. The interaction between the acid domain and the RING finger domain depends on its phosphorylation by ATM [78]. An increase of ATM-mediated phosphorylation has been also observed in hyperglycemia. Thus, it is not excluded that stress and the phosphorylation cascade induced by high glucose levels may phosphorylate some residues on the RING finger domain and/or on nearby regions and on the acid central domain in Mdm2 leading to the inhibition of p53 poly-ubiquitination and degradation.

Conversely, p53 ubiquitination also depends on ATP levels. In hyperglycemia conditions, ATP decreases due to increased ROS and mitochondrial uncoupling. Therefore, if ATP-decreased levels occur, ubiquitin ligases are unable to

condensate the glycine residues on their C-terminal region with the lysine residues on p53. Thus, it is necessary to analyze these factors in hyperglycemia conditions in order to know about its participation for p53 ubiquitination in RINm5F cells.

Cell Cycle Alterations

Cell Proliferation Rate

In obese subjects, β-cell failure to compensate for insulin resistance has been related to either an inappropriate cell mass expansion or the inability of preexisting cells to respond toward glucose. This may be generated from defects of insulin signaling or the absence of insulin receptors and IGF-I in these cells [64]. For instance, *knockout* mice for these receptors exhibit a decreased cell mass and develop diabetes from an early age. It has been pointed out that progression through the cell cycle is also altered. It has been observed that cyclin inhibitor p27kip1 is progressively accumulated inside β-cell nucleus in mice lacking the insulin receptor substrate-2 (IRS-2) and also in *db/db* mice. p27kip1 accumulation in oxidative stress and hyperglycemia conditions may be another pathway by which ROS decrease β-cell mass as the deletion of its gene hampers hyperglycemia effects and induce β-cell proliferation [79]. Another important regulator of β-cell replication is the cell cycle inhibitor p21, which is expressed at high levels in adult β-cells and it has been linked to proliferation decrease during senescence. It is known that β-cell replication potential is lost with age, and it is correlated with the loss of expression of genes such as EZH2 (enhancer of Zeste homologue 2), a histone methyl transferase that represses the transcription of cell cycle inhibitors when histone 3 is trimethylated in its lysine 27 residue (H3K27me3). EZH2 decreases H3K27me3 and increases p16 and p19 expression, and it inhibits β-cell proliferation [80].

β-Cell Dedifferentiation

During recent years it has been observed that pancreatic β-cells undergo a **dedifferentiation process** when metabolic demand increases and also during hyperglycemia and inflammation. In mouse, hyperglycemia modifies the expression of transcription factors and insulin secretion. For instance, the loss of FOXO1 leads to β-cell dedifferentiation, decreases insulin content, and reverts its phenotype toward progenitor-like cells, characterized by the expression of Ngn3. Although changes in transcriptional factors have been observed on humans and primates affected by diet-induced prediabetes, a dedifferentiation process has not been demonstrated. β-cell dedifferentiation induced by hyperglycemia is reverted when blood glucose values are restored. Insulin immunostaining loss correlates with an increased glucagon staining in several diabetic mouse models. In one of these, it was observed that small β-cells begin to express glucagon, although it is not known if these cells will transform into α-cells or if they represent an intermediate cell type expressing glucagon [56, 81]. The Pax4 gene also participates in β-cell dedifferentiation. The latter is an embryonic development regulator of pancreatic islets, and its presence on adult β-cells from animals confers protection against stress-induced apoptosis, and it stimulates cell proliferation. However, the sustained Pax4 expression promotes β-cell dedifferentiation and hyperglycemia. Pax4 overexpression is concomitant with Ngn3 expression. This suggests that an acute Pax4 increase protects cells but its steady or chronic expression induces β-cell dedifferentiation into progenitor cells apparently as a protective mechanism against deleterious environmental effects [82].

Adaptative β-Cell Proliferation

Adaptive β-cell proliferation has a very important role in delaying or preventing diabetes; this has been demonstrated in several models of mice whose β-cells have alterations in the replication pathway, which accelerates the development of diabetes in response to diets high in fat [83]. The adaptive expansion of the mass of β cells, in response to insulin resistance and hyperglycemia, may be due to hypertrophy, hyperplasia, and/or neogenesis [1].

The ability to adapt pancreatic β-cells to various adverse situations has been previously recognized. Studies in obese mice/OB C57BL/6J [84] and animal models of metabolic syndrome (dyslipidemia, insulin resistance, glucose intolerance, and hypertension) induced by the consumption of corticosteroids [85] or fructose [86] show an increase in the proliferation of β-cells and increase in the volume of the islet. These modifications resulted in an increase of insulin release despite marked apoptosis of β-cells [87].

In addition, it is known that the mass of pancreatic β-cells changes along the natural history of T2D. This was demonstrated at the rodent *Psammomys obesus*, which develops the disease in captivity and fed a high-fat diet. At the beginning, it has hyperinsulinemia/normoglycemia and insulin resistance; subsequently pancreatic β-cells die and hyperglycemia becomes evident [26]. These studies support the initial increase of cell proliferation rate and for a certain time in different models of metabolic syndrome, including carbohydrate consumption, as an adaptive response to stop the increase in plasma glucose by increasing insulin secretion [2, 88]. The presence of apoptosis has also been demonstrated [87], which can be increased if the stimulus persists (insulin resistance, chronic exposure to excess glucose and lipid) and then glycemia increases and diabetes is presented.

MicroRNAs in Pancreatic β-Cells Function and Dysfunction

miRNAS are small noncoding RNA molecules (21–23 nucleotides); those act as the main regulators of gene expression and control various biological and pathological processes. In humans, more than 1600 precursor miRNAs are known, which can produce up to 2237 mature miRNAs, each with the potential to control hundreds of targets. MiRNAs can be found and studied in blood and other body fluids associated with proteins, micro vesicles, and/or high- and low-density lipoproteins [89].

The miRNAs form a complex network that regulates the activities of β-cells and the compensatory response during pregnancy, obesity, and the development of T2D. Changes in the expression of miRNAs of β-cells and insulin target tissues have been observed in animal models of obesity and diabetes and even in the human pancreas from donors [90], which suggests its involvement in the early stages of diabetes.

In β-cells, miRNAs-375, miRNAs-7, and miRNAs-204 are regulators of multiple cellular functions and determinants of the balance between differentiation/maintenance of phenotype and cell growth/proliferation [91]. miRNA-375 regulates the expression of genes related to glucose-induced insulin secretion, Na+ channels, insulin exocytosis, phenotype, and β-cell expansion during insulin resistance. Circulating miR-375 represents 10% of the miRNAs present in β-cells; therefore it was proposed as a potential marker of β-cell mass in patients with IR and T1D [92, 93]. miRNA-375 also plays an important role in pancreatic organogenesis and in vitro differentiation of pancreatic β-cells. The overexpression of miRNA-375 together with let-7g, let-7a, miR-200a, and miR-127 in human embryonic stem cells derived from pancreatic progenitors promotes the exit of the cell cycle and its differentiation toward endocrine cells [94]. The miR-7 family (miR-7a-1, miR-7a-2, and miR-7b) [94] is also elevated in β-cells. miR-7a has been associated with decreased glucose-stimulated insulin secretion and loss of the β-cell phenotype in T2D models (Goto-Kakizaki rat) [95]. The expression of miR-204 is high in human pancreatic β-cells. A recent study demonstrated that the deletion of miR-204 in islets of *db/db* mice increases cell proliferation, decreases apoptosis due to ER stress, and increases insulin secretion [96].

In pancreatic β cells, some miRNAs are involved in the induction of apoptosis. Prolonged exposure to palmitate of MIN6B1 cells and islets of *db/db* diabetic mice increases the expression of miR-34a and miR-146, both related to an increase in the rate of apoptosis [97]. The increase in miR-34a is related to the activation of p53, whose participation in the apoptosis intrinsic pathway of β cells, was demonstrated in RINm5F cells [3, 69, 73]. p53 is also involved in the regulation of glucose metabolism and oxidative stress [98, 99]. Increases in miR-21, miR-34a, miR-29 and miR-146a, miR-335, miR-152, and miR-130a/b in animal models of obesity and T2D have deleterious effects on β-cells and are have been linked to insulin resistance [100]. An increase in the expression of miR-181 and miR-342 has also been reported in adult patients with glucose intolerance (IGT) and/or with loss of glucose sensitivity of β-cells. [101].

miRNAs also protect pancreatic β cells against oxidative stress. In islets of *db/db* mice and MIN cells subjected to oxidative stress, miR-24 expression increases and ER stress-induced apoptosis decreases [102]. This miRNA also promotes functional cellular dedifferentiation and decreases insulin synthesis. Therefore miR-24 can represent a central node to coordinate survival (inhibition of apoptosis) and the maintenance of a functional phenotype dedifferentiation [94]. The decrease in miR-184 protects β-cells from death by oxidative stress, in human islets cultured with palmitate or by exposure to inflammatory cytokines [103]. The genetic deletion of miR-200's family (miR-200c/miR-141 and miR-200a/miR-200b/miR-429) also protects against apoptosis in three experimental models of apoptosis [94].

Due to their multiple functions and their participation in the control of biological processes in β-cells, miRNAs are considered optimal therapeutic targets directed to multiple objectives such as the following. (a) Production of functional cells in vitro modulating the differentiation mechanisms of pluripotent stem cells (PSC), embryonic stem cells, or transdifferentiation of other types of adult cells into mature cells, to promote or to silence the expression of specific miRNAs according to the desired effect. Thus, for example, virus-mediated overexpression of miR-375 in iPSCs derived from human skin fibroblasts promoted their differentiation into insulin-producing cells and stimulated glucose-dependent insulin secretion in vitro [104]. (b) Protecting cells from glycolipotoxic and/or inflammatory stress, for example, increased miR-24 in MIN6 cells (mouse), protects against fatty acid-induced apoptosis and inflammatory stress [102]. Another possible therapeutic target is miR-184. Inhibition of miR-184 protects β-cells from apoptosis induced by glucolipotoxicity and inflammation and increases cell mass. Finally, miR-7 is a candidate to stimulate cell proliferation [103].

In general, miRNAs could be targeted to develop an effective therapeutic strategy against T1D and T2D. Therefore, various strategies have been developed to increase or decrease the expression and function of miRNA, such as transient or stable transfection or viral transduction of pri-miRNA, pre-miRNA, mature miRNA, small interference

RNA (siRNA), RNA of short hairpin, or antagomiRs [105]. However, the selective delivery of synthetic RNA molecules to a specific cell and avoiding side effects represents the main problem of RNA-based therapy.

Susceptibility of Pancreatic β-Cells to Infection by the SARS-CoV-2 Virus

The severe acute respiratory syndrome coronavirus two (SARS-CoV-2) is a respiratory virus that causes the COVID-19 disease, declared a pandemic in March 2020 by the WHO. The initial infection occurs through receptors present in the respiratory tract, where a first replication and the first manifestations of the disease take place, whose exacerbation or complication will depend on the presence of some comorbidities. Later, the virus can migrate and settle in other organs and continue its replication. The severity of COVID-19 has been attributed to the response of the immune system to restrain the infection and that it reacts disproportionately, triggering the so-called cytokine storm [106].

The SARS-CoV-2 virus has affinity for several receptors, most notably the receptor for angiotensin-converting enzyme 2 (ACE2). After binding with the receptor, the virus protein S is proteolytically activated by transmembrane serine protease 2 (TMPRSS2), among others [107]. Therefore, the expression of ACE-2 and TMPRSS2 is frequently used as a marker of susceptibility to direct infection by SARS-CoV-2 [108].

Although at the beginning of the pandemic, COVID-19 was identified as a respiratory disease; it is currently considered a systemic disease because patients infected with SARS-CoV-2 can present respiratory, cardiac, neurological, kidney, and endocrine disorders. The prevalence of metabolic disturbances such as ketoacidosis, hyperglycemia, and insulin resistance in patients with and without pre-existing diabetes, or the development of new-onset diabetes and frequent pancreatic lesions during COVID-19 disease, suggested that SARS-CoV-2 was capable of causing diabetes [109].

In the case of β-cells, the presence of the ACE2 receptor is still controversial [110]. Thus, some studies have demonstrated the presence of ACE2 and TMPRSS2 in human pancreatic β-cells [111, 112], while in other studies, it has not been proven [106, 113]. However, it has been proposed that the presence of additional factors such as neuropilin 1 and dipeptidyl peptidase-4 (among others), in human β-cells that are known to contribute to infection by the MERS-CoV virus could also help infiltration of the SARS-CoV-2 in β-cells [112].

SARS-CoV-2 infection of β-cells has been associated with decreased insulin levels and secretion, apoptosis [111], local inflammation, and necroptosis in pancreatic islets [112]. But due to inconsistent results about virus presence in β cells, it has been proposed that pancreatic damage and glycemic dysregulation may result from exacerbated systemic inflammation "cytokine storm." Pro-inflammatory cytokines (IL-1β, IL-6, IL-12, IFN-γ, and TNF-α) can drive β-cell dysfunction, damage, and death through intrinsic cell signaling pathways. What would increase the risk of developing autoimmune diabetes in individuals with genetic predisposition [108]?

The results on the expression of ACE2 in β-cells and the islet phenotype in COVID-19 show differences between individuals or under certain conditions. Therefore, it is necessary to analyze a greater number of histological samples from donors with COVID-19. Current data do not support constant large-scale β-cell injury that acutely leads to the development of diabetes. Therefore, it is essential to follow up patients recovered from COVID-19 for longer periods of time, to know the incidence of post-COVID-19 diabetes [108].

Conclusions

Obesity, resistance to insulin, and glucose intolerance affect pancreatic β-cell functional status. Particularly, the generation of new cells (**neogenesis**, replication) is decreased, whereas the apoptotic death rate increases. Among the mechanisms leading to β-cell alterations, the participation of several proteins synthesized by the cell itself, such as amyloid polypeptide and the type 2 uncoupling protein, the molecules expressed and released by adipose tissue (free fatty acids and cytokines), the presence of high glucose levels, and the reactive oxygen species produced by glucolipotoxicity has been observed. It was recently proposed that high-ROS-appearing levels during hyperglycemia promote phosphorylation, poly(ADP-ribosylation) and/or GlcNAc, and they may interfere with p53 degradation by inhibiting the Mdm2 E2 ubiquitin ligase. Therefore, p53 degradation is avoided, and its recruitment to mitochondria and the apoptotic mechanisms are promoted along with β-cell dysfunction.

The loss of β-cell mass may reach a critical point in which the deleterious effects mediated by the aforementioned molecules might not be reverted, thus decreasing insulin production and release and contributing to diabetes development. Several treatments exist in order to attenuate β-cell deterioration. Changes of dietary routine and increased physical activity are among them. The objective is to promote weight loss and specially to decrease abdominal fat and resistance to insulin. Thus, eventually β-cell mass may be regained.

Concluding Remarks

1. Activating hyperglycemia metabolic pathways induces β-cells apoptosis.
2. Free fatty acids are more toxic when hyperglycemia is present.
3. Oxidative and endoplasmic reticulum stress, mitochondrial alterations, inflammatory cytokines, and islet amyloid polypeptide, together or separate, can decrease pancreatic β-cell mass.
4. Hyperglycemia induces posttranslational changes in p53 that inhibits its degradation and promotes mitochondrial location.
5. Many factors trigger the death of pancreatic β-cells and decrease β-cell mass. However, most appear to have their origin in hyperglycemia, so the control of glucose levels is of great importance in preserving the mass and function of pancreatic β-cells.
6. miRNAs regulate the functions and survival of β cells, under different stimuli, so their use as therapeutic targets is being studied.
7. The expression of ACE2 in β-cells shows differences between individuals. Therefore, more studies are needed to determine the role of SARS-CoV-2 diabetes development.

Multiple-Choice Questions

1. At what stage of embryonic life is β-cell mass set?
   (a) Before birth
   (b) At 2 years old
   (c) While breastfeeding
   (d) **Between 5 and 10 years old**
   At this stage of development, the rate of cell replication is reduced and the pancreas reaches its full size.
   (e) At 5 years old
2. A diminution of B-cell mass was observed in persons without diabetes but with
   (a) Chronic hyperglycemia
   (b) Metabolic syndrome
   (c) **Impaired glucose tolerance**
   Postmortem studies in humans showed a decrease in pancreatic cell mass of up to 50% in people with impaired fasting glucose.
   (d) Obesity
   (e) Type 2 diabetes
3. All are apoptotic cellular death characteristics, except
   (a) DNA oligonucleosomal fragmentation
   (b) Phosphatidylserine exposition
   (c) Death cell phagocytosis
   (d) **Intracellular content release**
   An important characteristic of apoptosis is the formation of apoptotic bodies, which consists of the invagination of the plasma membrane that surrounds the subcellular remains and prevents the release of intracellular material.
   (e) Formation of apoptotic bodies
4. Increased production of reactive oxygen species in hyperglycemic conditions is due to
   (a) Microsomes
   (b) **Oxidative phosphorylation**
   Mitochondria are the main sources of endogenous ROS in hyperglycemic conditions. Of the oxygen consumed by mitochondria, ∼1–5% is converted to ROS as byproducts of the flow of electrons in the respiratory chain.
   (c) Macrophages
   (d) Endoplasmic reticulum
   (e) NADPH oxidase
5. Endoplasmic reticulum stress is characterized by
   (a) DNA oligonucleosomal fragmentation
   (b) Increased insulin demand
   (c) **Unfolded protein response**
   Constant requirements of insulin during glucose intolerance and insulin resistance leads to alterations in the processing of proteins in the RE. This situation stimulates an ER response known as unfolded protein response and ER stress.
   (d) Oxidative stress
   (e) Changes in mitochondrial permeability
6. In hyperglycemic conditions, p53-induced apoptotic β-cell pathway:
   (a) Releases intracellular content
   (b) **Changes mitochondrial permeability**
   P53 in the mitochondria releases Bax from Bcl-2, allowing Bax oligomerization and pore formation to release proapoptotic factors as cyt c.
   (c) Activates death receptors
   (d) Expresses proapoptotic proteins
   (e) Inhibits cell cycles
7. Hyperglycemia induces the activation of metabolic pathways related to β-cell death as
   (a) An increase in reactive oxygen species
   (b) Accumulation of amyloid polypeptide
   (c) Stress of the endoplasmic reticulum
   (d) A hexosamine pathway
   (e) **All of the above**
   During hyperglycemia, the activation of all these metabolic pathways was observed, which concluded with the activation of the intrinsic pathway of apoptosis.
8. What mitochondrial alterations contribute to the dysfunction of β-cells in diabetes?
   (a) **Fission and fusion events**

Hyperglycemia alters the expression of the proteins that regulate mitochondrial fusion/fission events, which modifies the $\Delta\Psi_m$ and allows the output of proapoptotic factors.

(b) Loss of glucose sensitivity
(c) Changes in ATP/ADP rate
(d) Increased proinflammatory cytokines
(e) Modification of NAD/NADH+ rate

9. Chronic hyperglycemia affects the survival of β cells by
(a) Decreasing beta-cell mass in diabetes by apoptosis
(b) Causing β-cell hyperplasia and exhaustion
(c) Causing cell dedifferentiation
(d) Creating a loss of glucose sensitivity
(e) **All of the above**

Chronic hyperglycemia decreases pancreatic β-cell mass by activating apoptosis and inhibiting the cell cycle, in addition to inducing the dedifferentiation of β-cells.

Glossary

Adipokines Cytokines (cell signaling proteins) secreted by adipose tissue.

Amylin A 37-amino acid peptide hormone, discovered in 1987, which is co-located and co-secreted with insulin by the pancreatic beta-cells in response to nutrient stimuli.

Antioxidant Molecule that inhibits the oxidation of other molecules.

Apoptosis (a-po-toe-sis) Was first used by Kerr, Wyllie, and Currie in 1972 to describe a morphologically distinct form of cell death and energy-dependent biochemical mechanisms.

Apoptosome Molecular complex of two major components—the adapter protein apoptotic protease activating factor 1 (Apaf1) and the pro caspase-9. These are assembled during apoptosis upon Apaf1 interaction with cytochrome c. Apoptosome assembly triggers effector caspase activation.

Cardiolipin Phospholipid important of the inner mitochondrial membrane, where it constitutes about 20% of the total lipid composition.

Caspase (cysteine-aspartic proteases, cysteine aspartases, or cysteine-dependent aspartate-directed proteases) Family of protease enzymes playing essential roles in apoptosis and inflammation.

Ceramides Family of waxy lipid molecules. A ceramide is composed of sphingosine and a fatty acid.

Cytochrome c Heme protein serving as electron carrier in respiration. Cytochrome c is also an intermediate of apoptosis.

Cytokines Cell signaling small proteins. Involved in autocrine signalling, paracrine signalling, and endocrine signalling as immunomodulating agents

Dedifferentiation process Processes by which cell that were specialized for a specific function lose their specialization.

Fission Division of mitochondria into new mitochondria.

Flavoprotein Proteins that contain a nucleic acid derivative of riboflavin: the flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN).

Fusion Process mediated by several large GTPases whose combined effects lead to the dynamic mitochondrial networks seen in many cell types.

Glucolipotoxicity Combined, deleterious effects of elevated glucose, and fatty acid levels on pancreatic beta-cell function and survival.

Hyperlipidemia Elevation of fats or lipids in the blood.

Hyperplasia Enlargement of an organ or tissue caused by an increase in the cell proliferation rate.

Inflammasome A multiprotein cytoplasmic complex which activates one or more caspases, leading to the processing and secretion of pro-inflammatory cytokines—e.g., IL-1 beta, IL-18, and IL-33. Assembly of inflammasomes depends on the NOD-like receptor family members, such as the NALP proteins kinase: enzyme-catalyzing phosphorylation of an acceptor molecule by ATP.

Misfolded proteins Are proteins structurally abnormal, and thereby disrupt the function of cells, tissues, and organs. Proteins that fail to fold into their normal configuration; in this misfolded state, the proteins can become noxious in some way and can lose their normal function.

Mitofusins Proteins that participate in mitochondrial fusion.

Necrosis Morphological changes in cell death caused by enzymatic degradation.

Neogenesis Generation of new cells.

Oxidative stress Pathological changes in living organisms in response to excessive levels of intracellular free radicals.

Proenzyme Precursor of an enzyme, requiring some change (hydrolysis of an inhibiting fragment that masks an active grouping) to render it active form.

Proteasome An intracellular complex enzymatic that degrades misfolded or damaged proteins (proteolysis), after damaged proteins are tagged by ubiquitin.

Resistance to insulin Pathological condition in which cells fail to respond normally to the hormone insulin.

RING finger domain Really interesting new gene-finger is a proteins domain that plays a key role in the ubiquitination process.

Stem cells Undifferentiated biological cells that can differentiate into specialized cells and can divide.

Sumoylation Small ubiquitin-like modifier (or SUMO) proteins are a family of small proteins that are covalently attached to and detached from other proteins in cells to modify their function. Post-translational modification involved in various cellular processes.

Triacylglycerol Ester of glycerol with three molecules of fatty acid.

Ubiquitin Small (8.5 kDa) regulatory protein that has been found in almost all tissues (ubiquitously) of eukaryotic organisms and regulated proteolysis.

Ubiquitin ligase Protein that recruits, recognizes a protein substrate, and catalyzes the transfer of ubiquitin from the E2 enzyme to the protein substrate.

Uncoupling proteins Proteins that uncouples phosphorylation of ADP from electron transport.

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Further Reading

Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005;54(6):1615–25. The author presents a unified mechanism that links overproduction of superoxide by the mitochondrial electron-transport chain to high glucose-mediated damage and diabetes complications. This paper provides the basis for understanding of the origin of ROS and oxidative stress in diabetes.

Grieco E, Brusco N, Licata G, Fignani D, Formichi C, Nigi L, Sebastiani G, Dotta F. Landscape of microRNAs in cell: between phenotype maintenance and protection. Int J Mol Sci. 2021;22:803–21. https://doi.org/10.3390/ijms22020803. This review is about the most important miRNAs regulating the maintenance and the robustness of β cell identity.

Hasnain SZ, et al. Oxidative and endoplasmic reticulum stress in b-cell dysfunction in diabetes. J Mol Endocrinol. 2016;56:R33–54. https://doi.org/10.1530/JME-15-0232. Here, the importance of deleterious effects of oxidative stress and endoplasmic reticulum stress-induced unfolded protein response is evaluated on β-cell insulin synthesis and secretion as well as on inflammatory signaling and apoptosis. Additionally, the authors describe recent findings on how inflammatory cytokines contribute to β-cell dysfunction and protect interleukin 22.

Hayden MR. An immediate and long-term complication of COVID-19 may be type 2 diabetes mellitus: the central role of β-cell dysfunction, apoptosis and exploration of possible mechanisms. Cell. 2020;9:2475–98. https://doi.org/10.3390/cells9112475. The author review COVID-19 participation on development of type 2 diabetes.

Hudish LI, Reusch JE, Sussel L. β Cell dysfunction during progression of metabolic syndrome to type 2 diabetes. J Clin Investig. 2019;129:4001–8. https://doi.org/10.1172/JCI129188. These authors focus on the current understanding from rodent and human studies of the progression of β cell responses during the development of MetS.

Kaufman B, et al. Mitochondrial regulation of β-cell function: maintaining the momentum for insulin release. Mol Aspects Med. 2015;42:91–104. https://doi.org/10.1016/j.mam.2015.01.004. Pancreatic β-cell function and insulin release is mitochondria dependent. In this work, the authors review mitochondrial metabolism and control of mitochondrial mass as they relate to pancreatic β-cell function.

Ortega-Camarillo C, et al. The role of p53 in pancreatic β-cell apoptosis. Immunoendocrinology. 2015;2:e1075. https://doi.org/10.14800/ie.1075. © 2015. This paper examines p53 mobilization to a mitochondrion and its phosphorylation, as well as the activation of the intrinsic route of β-cell apoptosis by hyperglycemia. They also describe how hyperglycemia affects the p53 degradation pathways.

Sharma RB, Alonso LC. Lipotoxicity in the pancreatic beta cell: not just survival and function, but proliferation as well? Curr Diab Rep. 2014;14(6):492. https://doi.org/10.1007/s11892-014-0492-2. This paper reviews free fatty acids' (FFAs) positive and negative effects on beta cell survival and insulin secretion. It also examines strong new findings that lipids may also impair compensatory beta cell proliferation.

Strycharz J, et al. Is p53 involved in tissue-specific insulin resistance formation? Oxid Med Cell Longev. 2017;2017:9270549, 23p. https://doi.org/10.1155/2017/9270549. The protein p53 is connected with metabolic defects underlying cellular aging, obesity, inflammation and β-cells apoptosis. Additionally, the authors discuss p53 regulation of multiple biochemical processes such as glycolysis, oxidative phosphorylation, lipolysis, lipogenesis, *β*-oxidation, gluconeogenesis, and glycogen synthesis.

Obesity in the Pathophysiology of Diabetes

14

Juan Antonio Paniagua and Antonio Vidal-Puig

Introduction: Obesity as a Public Health Problem

Obesity and overweight states are characterized by an excessive accumulation of body fat. Depending on the amount of fat accumulated, but also on the individual's genetic and exposure to specific environmental factors, the obese patient can develop several health problems. The increase in the prevalence of obesity and associated complications is considered a major public health issue that affects all demographic groups, irrespective of age, sex, race, education, or economic level [1]. The World Health Organization (WHO) estimates that more than 1.9 billion adults (≥18 years old) were overweight, and of these over 600 million were obese, according to the worldwide data registered in 2014 [2]. In the United States, obesity rates have been rising in both adults and children in recent years [3–5]. The maintenance of a healthy weight, usually achieved between 18 and 25 years of age, requires a life-long sustained energy equilibrium between energy intake and energy expended, which is affected not only by diet but also age, stage of development, genetic makeup as well as epigenetic, level of nutritional education, and physical and psychosocial interactions [6, 7].

A useful tool to define a person as obese or underweight is the body mass index (BMI), estimated by the relationship between weight and height. The age-standardized death rate, from any reason, was generally lowest in subjects with a BMI of 22.5–24.9 kg/m^2 [8–10]. Moreover, deaths associated with high BMI are ranked fourth, behind deaths from hypertension, smoking, and unhealthy diets and ahead of deaths related to hyperglycemia, sedentary life style, high-salt intake, alcoholism, and high blood cholesterol levels [11]. Lastly, it is also of relevance that the association between nutrient intake and diseases such as cancer, diabetes and cardiovascular disease (CVD) [12, 13], obesity, body fat distribution, hypertension, insulin resistance, and hyperglycemia is well established [14–16].

Deaths from CVD, cancer, and diabetes account for approximately 65% of all deaths, and obesity, mainly abdominal adiposity, increases the risk of all these disorders. BMIs higher than 25 kg/m^2 have a direct relationship with mortality due to CVD [6, 17–21]. CVD accounts for about 38.5% of all deaths in EE.UU. Of relevance, this figure has declined since the 1940s and 1960s [8], associated with several primary prevention activities, improved treatment for acute ischemic phase, and secondary intervention [22, 23].

Deaths from all cancers accounted for about 23% of the total [8]. As high BMI increases mortality from cancer in most specific sites [10, 24, 25], compared to people with normal weight, obesity could increase cancer incidence about 14% in men and 20% in women. People with BMI ≥ 40 kg/m^2 could increase risk of death from cancer up to 52% in men and 62% in women [26]. Higher circulating glucose levels, low-grade inflammatory state, increased oxidative stress, and an altered bioavailability of hormones, mainly insulin, estrogens, and androgens, could be implicated in the rise in current cancer rates obesity-related. Finally, during the 1990s, in the United States, there was an increase of diabetes prevalence to 61%, and of this ≈90% were type 2 diabetes (T2D), in parallel with increase in the obesity rates [27]. Diabetic patients have 2–4 times higher risk of incidents of CVD [28]. Recently, global mortality directly related to dia-

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betes was observed to be 2.9 million, about 5.2% of all deaths. Of this 2–3% was observed in the poorest countries, and over 8% was in the United States, Canada, and the Middle East. In people aged 35–64, this rates increased from 6 to 27% [29].

In the United States, approximately 70% of T2D patients are overweight and obese, and over a period of 10 years, the risk of diabetes rose to 27% in people who gained 5 kg or more [30]. Specifically, central obesity is strongly related with metabolic disorders associated with insulin resistance and diabetes [31, 32]. The current advice to prevent and treat T2D includes maintaining an ideal body weight (BMI < 27–30 kg/m^2), physical activity, limiting the intake of sugar and saturated fat, and increasing the consumption of mono and PUFA, as well as whole grains and fiber [33–35].

Obesity: Measurements and Assessment

Measuring body weight provides a sense of the degree of obesity; however, a more accurate and comparable measure of obesity is obtained by relating body weight to height [36]. The BMI is calculated as the ratio between weight/height squared ratio, and expressed as kg/m^2. Based on the BMI measurement, it can be discriminated low, normal weight, overweight, and obese states in adults. The WHO has standardized BMI as (1) lower than 18 kg/m^2 as low weight; (2) between 18 and 25 kg/m^2 is normal weight; (3) between 25 and 29.9 kg/m^2 is overweight; (4) greater than or equal to 30 kg/m^2 is obese [37, 38]. However, the BMI does not provide information about body composition (fat-free muscle mass/fat mass) nor about the pattern of body fat distribution. Thus, a better measure of obesity that overcomes these limitations are the measurement of percentage of body fat (BF%), which relates total weight to the weight of the fat mass. Of course, this is more difficult to measure than the BMI, limiting its daily clinical use, but several accurate methods exist [39]. Body composition can be estimated from anthropometric measurements of skinfold thicknesses in several anatomical regions [40]. In research, BF% is determined by hydrostatic weighing (body weight by immersion) as the gold standard [41]. Alternatively, the bioelectrical impedance analysis technique can directly estimate the amount of the fat-free mass (FFM) and indirectly the body fat by subtracting from total body weight [42]. Individuals with normal weight or overweight but also have a high BF% exhibit a cardiovascular risk which is comparable to those with obesity estimated by BMI. Of note, it is observed that at the age of 20, a BMI equal to 30 kg/m^2 implies a 30% of BF%. However at the age of 60, the same BMI represents a 40% BF% in men and up to 40–50% BF% in older women [43].

BMI informs neither the location nor distribution of the excess body fat. Central obesity occurs when the excess of fat accumulates in the intrabdominal area, even at the expense of a decreased fat accumulation in the peripheral adipose tissue. Several parameters can be used to measure central obesity. The most widely used requires measuring the waist circumference (WC) and hip ratio (HR) to create the waist-HR (WHR) ratio. Subjects having a large WC have increased mortality [44] despite having a BMI < 30. Thus, high-risk individuals are better identified by incorporating WC and WHR measurements to BMI [45]. The WC measurement of central obesity varies with race and is currently accepted as >88 cm in women and >102 cm in men in United States [46]. Finally, the relationship of waist circumference to height (WHtR) can also be used to identify adults at high cardiometabolic risk [47–49]. All these parameters help also to predict the risk of metabolic diseases such as T2D [50].

In research-intensive settings, more complex and accurate techniques are available, such as dual energy X-ray absorptiometry (DEXA), computed tomography (CT), and magnetic resonance imaging (MRI). DEXA estimates body fat distribution by scanning the arms, legs, and trunk [51, 52]. Differentiation between abdominal subcutaneous fat and intraabdominal fat, which is composed of visceral adipose tissue (VAT), intraperitoneal and retroperitoneal fat, is better seen by MRI and CT [53, 54]. Finally, single-voxel magnetic resonance spectroscopy is the gold standard for measuring ectopic fat, outside anatomically defined fat depots. Ectopic fat can be estimated after separating water and fat signals within each voxel (using software such as jMRUI) [55, 56].

Adipocyte and Adiposity Development

Types of Adipocytes and Differentiation

When describing fat depots, it is important to differentiate two types of well-differentiated adipose tissues, which have specific distribution and function, and are referred to as white adipose tissue (WAT) and brown adipose tissue (BAT) (Fig. 14.1). The WAT's main function is the deposit of surplus energy as triacylglycerol (fat), which could be mobilized and offered to other metabolically relevant organs through hormonal signaling. The WAT is designed to be plastic and expand. In fact, WAT accounts from 5 to 50% of human body weight. However, WAT is also a main source of endocrine signalling [67]. One of the key hormones is adiponectin, typically associated to the metabolically "healthy" expansion of adipose tissue facilitating adipocyte lipid storage and consequently preventing ectopic lipid accumulation. Conversely, leptin prevents lipogenesis while facilitating lipolysis and fatty acid oxidation. These actions may be mediated centrally by the activation of sympathetic efferent

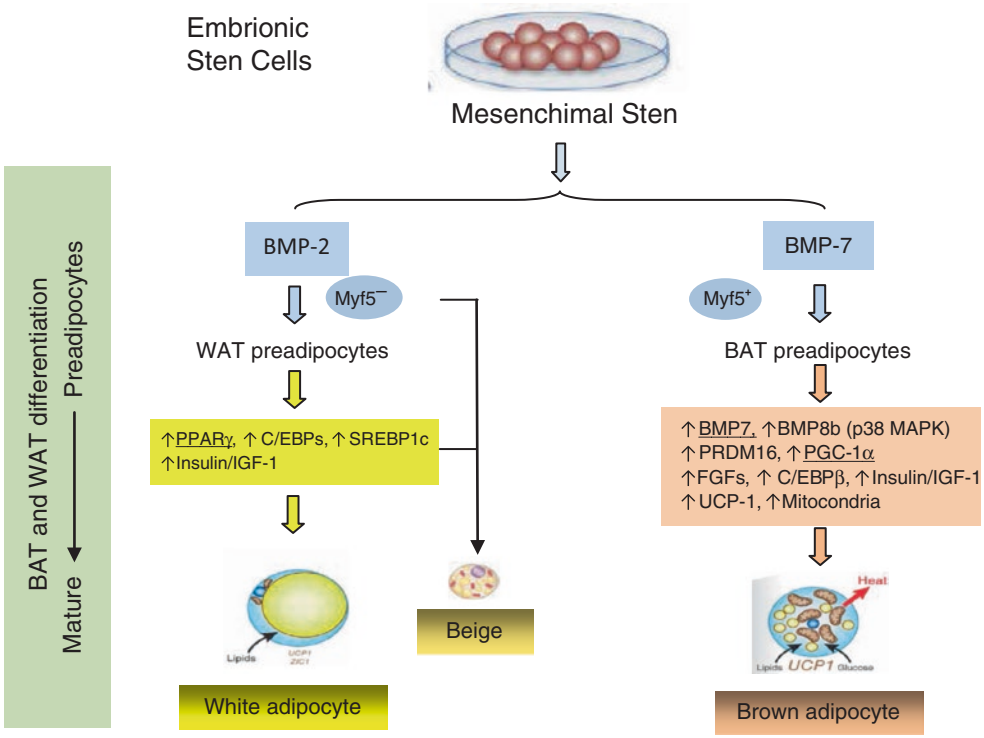

Fig. 14.1 Adipose tissue expands to store excess energy as fat and regulates fuel needs to other tissues. In WAT growth transcriptional factors such as the binding proteins CCAAT/enhancer (C/EBP) and PPAR-γ are fundamental. Sterol regulatory element-binding transcription factor 1 (SREBP1c) activates PPAR-γ expression [57] and mediates lipid biosynthesis by insulin [58]. Mature WAT is characterized by the expression of glucose transporter 4 sensitive to insulin (GLUT4) and enzymes like fatty acid synthase (FAS) and glycerol-2-phosphate dehydrogenase [59, 60]. During adipose tissue expansion, inappropriate vascular tissue development results in hypoxia and death of adipocytes, and macrophage infiltration is induced [61]. On the other hand, BAT derived from Myf5⁺ mesoderm progenitors shares a common origin with skeletal myoblasts [62]. The development of BAT requires that PRDM16 activates PPAR-γ coactivator (PGC-1α/β) or CtBPs and inhibits transcriptional factors that induce WAT [63, 64]. In addition, bone morphogenetic protein 7 (BMP-7) turn on a full program of brown adipogenesis involving induction of PRDM16 and PGC-1α and expression of UCP-1 which is a feature of brown cells [65]. Last, beige fat cells adapt functions, either like "WAT" when energy balance is exceeded, or like "BAT" in response to stimuli similar to BAT activation. Today, research in identifying the main genes that control differentiation, development, and activation of BAT is highly active. This work is licensed under a Creative Commons Attribution-NonCommercial (CC BY-NC 4.0) International License [66]

signals to both brown adipose tissue and WAT to induce lipolysis. Leptin has recently been suggested as therapy for individuals with generalized lipodystrophy, who frequently develop severe metabolic syndrome characterized by hepatic steatosis, insulin resistance, and diabetes mellitus.

The physiological expansion of WAT involves different degrees of hypertrophy and/or hyperplasia of adipocytes, and active remodeling of vascular and mesenchymal stromal cells. Also immune cells, endothelial cells, and undifferentiated or adipocyte precursor cells (APs) must also be coordinately developed [68]. Storage of excessive fat in WAT causes mechanical overload and contributes to increased risk of metabolic disorders. The repertoire of molecules secreted by adipocytes is not exhausted. Recently asprosin was described to be abundantly expressed in mature white adipocytes, accumulated in excess in the blood of humans with obesity and proportional to insulin levels, which has suggested asprosin levels may be associated with insulin resistance [69].

The role of BAT is thermogenesis contributing to energy expenditure and body weight regulation (Fig. 14.2) [70, 71]. In mammals, BAT is the primary site of thermogenesis in the absence of muscle contraction. BAT thermogenic function is mediated by the activation of a specific mitochondrial uncoupling protein 1 (UCP1) (Fig. 14.2). In humans, BAT function is particularly important for the control of body temperature after birth and in early childhood [72]. However, data from adipose tissue samples together with evidence provided by positron emission tomography coupled with computed tomography have established the existence of functionally active brown adipose tissue in adult humans [73–76]. Furthermore, some of these studies also relate the degree of activation of these sites with BAT and lower BMI, increased basal energy expenditure, and decreased onset of diabetes [77]. BAT in adult humans can be found in the cervical and supraclavicular [78] regions, depots identified as canonical BAT exhibiting similarities with the BAT in rodents. Lastly, recent studies have reported on secretory molecules from

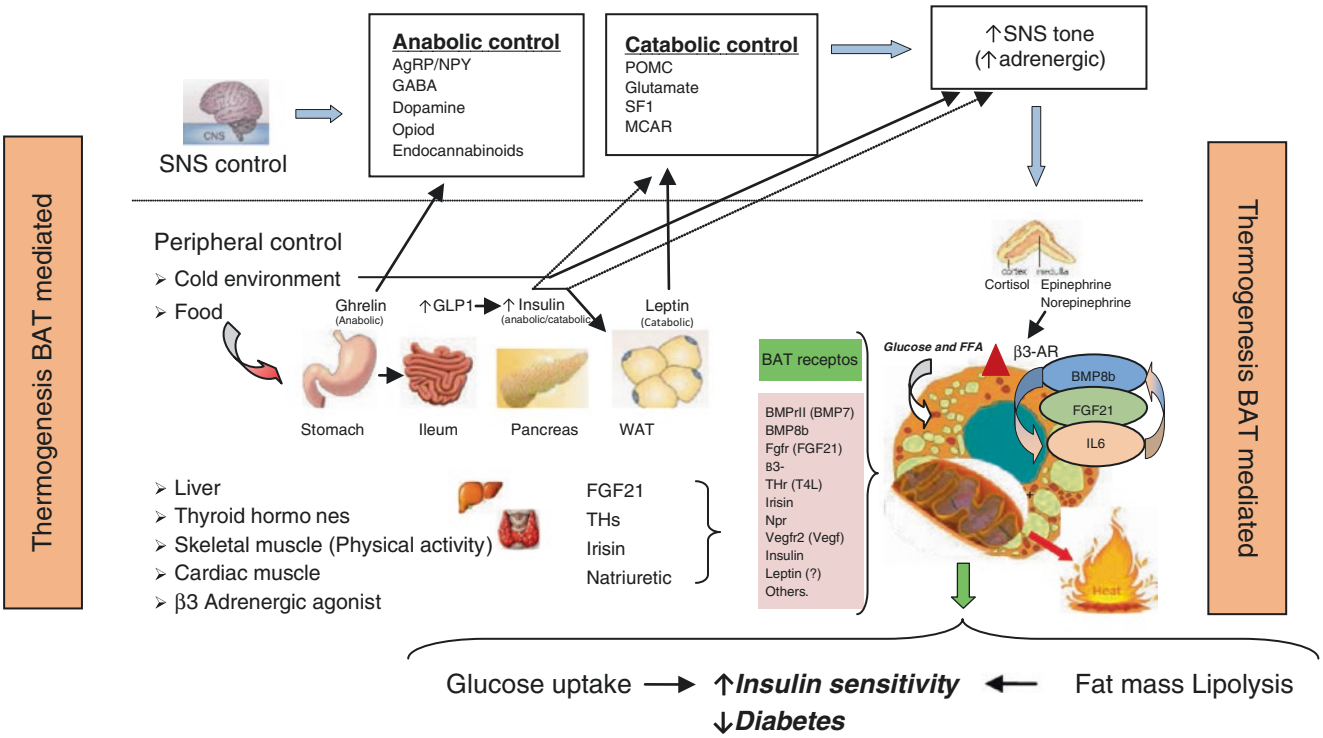

Fig. 14.2 By contrast to WAT, brown adipose tissue (BAT) was developed especially for energy expenditure (thermogenesis) mainly controlled by the SNS, which highly innervates brown fat cells. BAT is regulated in response to cold temperatures, hormones, and diet. BAT abundance and activation is highest in children and decreases with age. BAT activity decreases with BMI, body fat, and visceral obesity. Of note, BAT activity is lower in diabetics than nondiabetic subjects. Thyroid hormones play a key role in controlling BAT activation, such as the cold-induced deiodinated thyroxine (T4) to the more active T3. Norepinephrine binds to β-ARs inducing PGC1α and expression of UCP1. Whereas β1-AR mediates precursors of BAT proliferation, β3-AR plays a key role in the thermogenic function of BAT. Another signal, Irisin hormone, released from muscle to fat tissue, mediates the beneficial effects of exercise reducing diet-induced obesity and improving insulin resistance. In addition, FGF21, secreted by adipose tissue, liver and skeletal muscle, regulates lipolysis in WAT and increases substrate utilization by increasing fatty acid oxidation in the liver. This actions may be mediated increasing activity of adiponectin. *WAT* white adipose tissue, *BAT* brown adipose tissue, *PRDM16* PR domain-containing 16, *PPAR-γ* peroxisome proliferator-activated receptor-γ, *PGC-1α* peroxisome proliferator-activated receptor γ coactivator 1α, *SNS* sympathetic nervous system, *BMI* body mass index, *FGF21* fibroblast growth factor 21.

BAT, the so-called batokines, which include fibroblast growth factor 21 (FGF21), neuregulin 4 (NRG4), vascular endothelial growth factor A (VEGFA), and bone morphogenetic protein 8B (BMP8B). These studies indicate that similar to WAT, the BAT may also play a physiological role as an endocrine organ [79].

On top of white and brown adipocytes, a third fat cell named beige/brite, which shares similarities with brown adipocytes, is found infiltrating skeletal muscle as well as in diverse areas of WAT [80]. Of note, beige cells are Myf5-positive cells, a classical feature of BAT, and appear dispersed in WAT [81]. The term "beige" describes their similar morphology with white adipocytes, but the inducibility of features similar to brown adipocytes including UCP1 activity with β-adrenergic stimulation [82, 83]. There is also evidence that beige mature adipocytes can be interconvert between typical white or brown adipocytes, without the need for de novo cell differentiation from precursors cells [83]. A priori, this could mean that the rate of lipid storage or lipid oxidation could be adapted and adjusted in response to external stimuli such as a decrease or increase in temperature. Results from mice indicate that activated beige cells may contribute to improve carbohydrate metabolism and prevent/reverse fatty liver [84]. In any case, the physiological relevance of these cells in humans is far from being confirmed.

Effects of Hormones and Adipokines on Adipogenesis and Glucose Metabolism

Adipose tissue development and function are modulated by hormones and growth factors, secreted molecules by adipose tissue cells, and by nutritional factors and pharmacological drugs (Fig. 14.2).

Hormones and Growth Factors

Insulin is the key anabolic hormone that contributes to adipocyte differentiation and lipogenesis [85]. Brown preadipocyte determination is also regulated by insulin through a necdin-E2F4 interaction that represses peroxisome proliferator-activated receptor-γ (PPAR-γ) transcription [86]. When in excess hyperinsulinemia either exogenously or endogenously is a major enabler of adipose tissue expansion contributing to weight gain. Several molecules produced by cells from the adipose tissue such as tumor necrosis factor alfa (TNF-α), leptin, and resistin interact and inhibit insulin signaling on adipocytes.

Glucocorticoids and sexual hormones also affect the functionality and development of the adipose. For instance, the infusion of hydrocortisone increases levels of circulating free fatty acids (FFAs) by activating the mechanisms of lipolysis [87, 88]. Glucocorticoids promote adipogenesis by increasing the expression of both PPAR-γ transcription factors and C/EBPδ and decreasing the expression of pref-1 [89]. The adipocyte also has a complete arsenal of enzymes that regulate the metabolism of steroid sex hormones [90]. Glucocorticoids control the activity of 11-β-hydroxysteroid dehydrogenase 1 and 2 (11 βHSD1 and 2) that can change the active-form cortisol to inactive cortisone and vice versa [91]. Of note this enzyme is highly expressed in visceral adipose tissue which may contribute to the regional redistribution of fat [92, 93]. Another key aspect related to adipose tissue distribution in sex steroids. Body fat distribution is different in men and women, and adipose tissue has activity of either cytochrome P450-dependent aromatase or 17-β-hydroxysteroid dehydrogenase (17βHSD) enzymes that can modify the repertoire of steroids. Aromatase mainly regulate the rate of transformation of androgens into estrogens, while 17βHSD regulates the formation of a more active form of androgens. Of note, the ratio 17βHSD/aromatase in adipose tissue correlates directly with central obesity [90, 94].

Thyroid hormones are main contributors to global growth and development [95] by exerting an important role-controlling energy metabolism and the function of the main metabolic organs such as the adipose tissue, liver, heart, skin tissue, or muscle [96, 97].

Growth hormone and insulin-like growth factor 1: Growth hormone (GH) is critical for somatic growth but also has enormous influence of the regulation of body fat composition and distribution, through its lipolytic and anabolic effects [98].

Adipocytokines: Adipose tissue contributes to the metabolic control of energy substrates such as glucose and lipids and interacts with several hormonal systems. The molecules produced by adipose tissue (adipokines) act in many organs including the adipose, muscle, and CNS. In obese and insulin-resistant patients, there are qualitative and quantitative changes in the repertoire of adipokines. For example, some adipokines increase (e.g., leptin, resistin), while others decrease (e.g., adiponectin) (Figs. 14.2 and 14.3) [111].

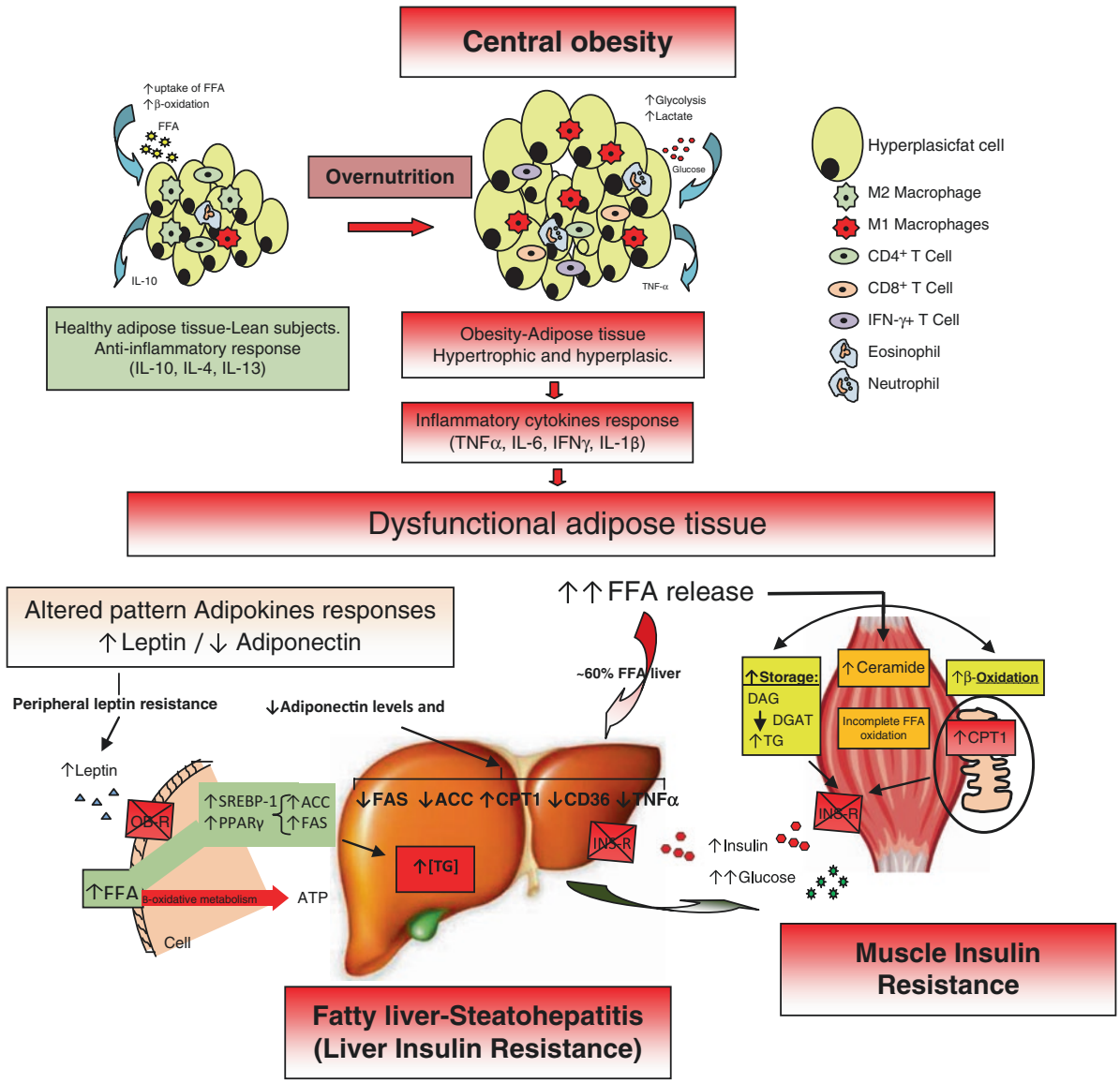

Fig. 14.3 Dysfunctional adipose tissue. When adipose tissue expands, it is slowly infiltrated by macrophages, and a low-grade chronic inflammatory state is developed [99, 100]. Several macrophage subtypes can be seen, which can be divided into pro-inflammatory M1 or alternatively activated M2 [101]. Adipocytes, macrophages, and immune T cells contribute to the production of inflammatory cytokines [99, 102–104]. The M1 macrophages are induced from precursor M0 macrophages by stimulation of type 1 T-helper (Th1) inflammatory cytokines like IFN-γ and TNF-α and lipopolysaccharide, whereas the M2 macrophages are induced by type 2 (Th2) cytokines such as IL-4 and IL-13. While adipose tissue of obese subjects show mainly M1 macrophages, lean subjects have high levels of M2 macrophages. M2 macrophages are involved in remodeling and tissue repair through the action of IL-10, IL-1 receptor antagonist, and arginase-1, which result in better insulin sensitivity. Whereas M1 macrophages use glucose for energy, M2 macrophages activate the β-oxidation of fatty acids [101, 105]. Finally, M1 macrophages are a principal source of TNF-α which, by activating Wnt signaling and suppressing expression of PPAR-γ, interferes with the development and function of adipocyte and reduces the capacity to store triglycerides [106, 107]. Peripheral adipose tissue will expand to an equilibrium point, and when exceeded (inflexibility), glucose and lipid uptake decline, while insulin levels rise in order to maintain serum glucose within the normal range [108]. In addition, inflexibility is associated with early insulin resistance which increases lipolysis in adipose tissue, generating a redistribution of fats with systemic lipotoxic effects in the muscle, liver, β-cell, etc. (lipotoxicity). Furthermore, increased TNF-α and IL-6 levels are inversely related with peripheral and hepatic insulin-mediated glucose-uptake [109]. The liver takes up excess released FFA in serum to capacity by storing with glycerol (TAG), and the slowly fatty liver could be developed (NAFLD). Peripheral FFAs contribute ~60% of total TAG stored in the liver, whereas the novo lipogenesis is ~26% and ~15% is from food [110]. On the other hand, leptin levels rise with adipose expansion, while adiponectin levels tend to decrease. The elevated leptin levels should increase β-oxidation in non-adipose tissues, decreasing excess fatty acids in these cells. However, this action may be partially blocked by the anabolic effect of hyperinsulinemia, inducing a leptin system dysfunction (peripheral leptin resistance) [111]. In addition, adiponectin action improving peripheral glucose uptake and adiponectin protective action on liver fat accumulation are decreased [112]. Finally, both leptin and adiponectin seem to regulate the deposition of fat in insulin-sensitive tissues by increasing β-oxidation. *IFN-γ* interferon-γ, *TNF-α* tumor necrosis factor-α, *IL* interleukin, *PPAR-γ* peroxisome proliferator-activated receptor-γ, *WAT* white adipose tissue, *FFA* free fatty acids, *NAFLD* nonalcoholic fatty liver disease, *CPT-1* carnitine palmitoyltransferase-1, *FAS* fatty acid synthase, *ACO* acetyl-CoA carboxylase.

Major Adipokines

Leptin: Leptin is secreted by adipocytes, establishing a negative feedback between the amount of adipose tissue and satiety centers in the brain [113, 114]. Leptin also serves as a sensor of energy availability enabling energy demands such as pregnancy and adaptation to starvation [115]. Leptin levels decrease after weight loss, enabling saving energy adaptive response involving low-thyroid activity, sympathetic tone, and decreased basal energy expenditure [116]. Thus, treating leptin deficiency with recombinant leptin not only reduces food intake and body weight [117] but also reverses infertility, prevents lipodystrophy associated metabolic complications, and reverses impaired glucose metabolism [118–121]. The leptin action appears to be facilitated by insulin, glucocorticoids, TNF-α, estrogens, and C/EBPα and is decreased by androgens, β3-adrenergic activity, GH, FFAs, and PPAR-γ agonist [122].

Leptin also plays an essential role in energy metabolism, by facilitating lipid mobilization and preventing ectopic fat accumulation (lipotoxicity syndrome) [123, 124]. Leptin facilitates lipid oxidation and by doing so can reduce excessive fatty acid accumulation in the liver, pancreas, heart, kidney, and muscle tissue (Figs. 14.2 and 14.3).

Adiponectin: Adiponectin is produced in mature adipocytes and is more abundant in peripheral subcutaneous than visceral adipose tissue [125]. Adiponectin receptors are G protein-coupled highly expressed in muscle (AdipoR1) and liver (AdipoR2) [126]. Through them adiponectin promotes lipid oxidation in the skeletal muscle and liver and reduces hepatic glucose production and postprandial hyperglycemia [112, 127] contributing to maintain metabolic homeostasis.

Adiponectin deficiency, as observed in obesity, plays a role in the development of insulin resistance and type 2 diabetes as suggested by the following: (a) Adiponectin levels have an inverse relationship with the degree of obesity, insulin resistance, and T2D [128, 129], which is reversed by adiponectin treatment which results in the improvement of IR [130]. (b) Adiponectin reduces FFA levels and is associated with improved lipid profile, glycemic control, and reduced inflammation in T2D patients [131]. (c) TNF-α plasma levels and its hepatic production are decreased by adiponectin treatment, which also improved hepatomegaly, steatosis, and ALT levels related with nonalcoholic fatty liver disease (NAFLD) (Fig. 14.3) [112]. (d) The PPAR-γ agonists (thiazolidinediones, TZDs) redistribute lipids from central to peripheral depots and also increase adiponectin levels, and improve lipid profile and insulin sensitivity, while improving diabetes and NAFLD [132]. This suggests that maintaining normal levels of adiponectin may help in the treatment of early-stage diabetes. However, the relationship between adiponectin levels and cardiovascular disease is not well established [133].

Other Adipokines

Resistin has also been related to obesity, insulin resistance, and development of T2D. Blocking the action of resistin improves insulin sensitivity [134]; however, the significance of resistin in glucose metabolism in human still is inconclusive.

Visfatin is produced predominantly by abdominal adipose tissue and has been suggested to have insulin-mimetic actions [135, 136]. However, the importance of visfatin in glucose metabolism is still unclear [137].

Omentin 1: Obesity decreases both omentin plasma levels and omentin gene expression in visceral adiposity [138]. In obese women with polycystic ovary syndrome (PCOS), glucose and insulin levels were negatively related with omentin 1 levels, whereas metformin treatment increased serum omentin levels in parallel with improvements in insulin sensitivity and glycemic control [139, 140].

Obestatin is a hormone that opposes the effects of orexigenic effect of ghrelin. Obestatin decreases in subjects with diabetes and impaired glucose tolerance [141], and its receptors are downregulated in obesity-associated T2D [142].

Retinol-binding protein 4: Retinol-binding protein 4 (RBP4) is released from adipocytes and correlates with the degree of insulin resistance in obesity, T2D, and relatives of T2D patients [143–145]. The specific role of RBP4 in insulin resistance has not been determined.

Asprosin is a 140-amino-acid polypeptide, recently described, abundantly secreted, and expressed in WAT. Levels of asprosin are increased in fasting situations in healthy humans. Asprosin acts on the liver, stimulating hepatic glucose production. Asprosin administration induces a quick increase in plasma levels of glucose and insulin. Blocking asprosin actions might be beneficial for the treatment of type 2 diabetes mellitus [69].

Inflammatory Adipokines

TNF-α is a transmembrane protein released mostly by activated macrophages and also by other cell types including endothelial cells, adipocytes, etc. (Fig. 14.3) [146–148]. Both TNF-α gene and its receptors are present in adipocytes and are expressed at higher levels in WAT [125]. TNF-α contributes to local and systemic inflammation, which limits the proliferation and differentiation of mature adipocytes. Increased release of TNF-α from adipose tissue contributes to the impairment of insulin action [102, 149, 150], and treatment with anti-TNF-α antibody led to improvement in glucose utilization in obese rats [102] at least. Similarly, obese mice genetically modified to ablate TNF-α had close to normal insulin sensitivity [150]. Moreover, weight reduction is associated with both improved insulin activity and

decreased TNF-α gene expression [151]. The mechanism how TNF-α promotes insulin resistance may involve the decrease in the expression of PPAR-γ and target genes involved in lipid and glucose uptake [152, 153]. A link between fatty acid-binding protein 4 (aP2), FFAs, and increased expression of TNF-α in obesity has been suggested [149]. Not only TNF-α but also interleukin-6 (IL-6) were both increased after nutritional fatty acid activation of Toll-like receptor 4 (TLR4) [154].

IL-6 is secreted by adipose tissue, T cells, and macrophages (Fig. 14.3). Adipocytes can produce IL-6, which is associated with C-reactive protein (CRP) levels and inflammatory states typically found in obese patients [155]. About 1/3 of the total concentration of IL-6 is produced in adipose tissue, mainly by visceral adipose tissue compared with peripheral adipose tissue [125]. It has been suggested that IL-6 levels are directly linked to obesity and insulin resistance [156] and to the inhibition of the activity of lipoprotein lipase (LPL) [157].

Chemokine molecules are potent chemo attractants of leucocytes and modulate the formation of reactive oxygen and cytokines. The chemokine molecule 5 (CXC ligand 5, CXCL5) is expressed at high levels by the macrophage of white adipose tissue [158]. Serum levels of CXCL5 are elevated in obese patients independently of their degree of insulin resistance above the levels observed in normal-weight subjects [158]. Furthermore CXCL5 serum levels are reduced after weight loss.

Fatty Acid Metabolism Effects on Adipogenesis and Glucose Metabolism

FFAs are energy-rich molecules which are fundamental regulators of metabolism. Excess calories ingested as fat, protein, and carbohydrates end up stored as triglycerides in white adipocytes. FFAs are also essential constituents of the cell membrane, influencing its fluidity and the topology of receptors, transporters, and other membrane proteins. In addition, FFAs can have hormone-like actions and serve as ligands of nuclear receptors controlling gene expression [159]. Although food is the main source of essential fatty acids, de novo endogenous biosynthesis could supply nonessential fatty acids [160].

Both linoleic acid (ω-6 series) and linolenic acid (ω-3 series) have been related to decreased insulin resistance and CVD and must be included in the diet [161]. By contrast, excess saturated fatty acids and trans fats in the diet is associated with increased insulin resistance and risk of CVD [161].

LPL activity is increased by insulin and depends on apo CII and apo CIII being released by adipocytes. LPL is essential for FFA uptake from lipoproteins and storage [162]. In addition, cytoplasmic fatty acid-binding proteins (FABPs) facilitate intracellular transport and partition of FFA to specific compartments and functions [163]. FABPs link lipid metabolism, hormone action, and systemic energy homeostasis involving glucose metabolism [149].

De novo biosynthesis of saturated chain fatty acids is carried out mainly in the liver where acetyl-CoA is formed from pyruvate. Most de novo FFA are synthesized from acetyl-CoA and malonyl-CoA through two enzymatic steps, including acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS). The ACC controls production of short fatty acids which are elongated until 16-carbon palmitic acid is formed by FAS (cytosol). Nearly all fatty acids required can be synthesized from palmitic acid by several steps of oxidation and elongation [164]. Finally, various enzymes which regulate the synthesis of triglycerides are also implicated in glucose metabolism [165]. Overexpression of diacylglycerol acyltransferase 1 (DGAT1) results in increased adipose tissue without affecting IS but increases the secretion of TNF-α [166]. A remaining question is whether de novo lipogenesis-originated fatty acids may have a specific fate or contribute to specific functions different from the pools of FAs generated from dietary nutrients.

Obesity Effects on the Pathogenesis of Type 2 Diabetes

Type 2 diabetes (T2D) mellitus is characterized by hyperglycemia, insulin resistance, and inappropriately low secretion of insulin. The prevalence of T2D has increased in parallel with the increased prevalence of obesity [167] and sedentary lifestyle [168]. The pathogenesis of common forms of T2D is complex [169], requiring the combination of different degrees of insulin resistance and insulin deficiency [170]. In addition, insulin resistance and defects in insulin secretion can be determined via genetic and/or varying environmental factors, complexity that makes difficult to isolate a single cause in diabetic patients [171]. However, it is clear that the final development of diabetes requires beta cell failure as suggested by the fact that obese subjects do not necessarily develop T2D.

The potential molecular links between obesity and increased risk of T2D include exacerbated inflammatory response with excessive cytokine secretion (TNF-α and IL-6), insulin resistance, defects in fatty acid metabolism and lipotoxicity, mitochondrial dysfunction, and endoplasmic reticulum stress. However, weight loss is a central intervention working on most forms of prediabetes, because even modest weight loss improves glycemic control and reduces diabetes risk.

The risk of T2D and cardiovascular disease rises with the amount of body fat, and more particularly when fat accumulates in the central or abdominal depots [172]. Whether subcutaneous fat deposition is less pathogenic than visceral fat is quite likely but requires further investigation. In addition, the contribution of the subtypes of adipose tissue to glucose metabolism is important. For instance, increased level of brown adipose tissue may help to control carbohydrate metabolism and prevent or reverse obesity [73, 173].

Infiltration of immune cells in adipose tissue can alter its metabolic functions. Although the adipose tissue is not the cause of obesity per se, taking advantage of the specific functions of the repertoire of fat cell types and functional characteristics of the depots including the immune cells may help to uncouple obesity from its complications.

The main proposed mechanisms linking obesity to insulin resistance and T2D include (1) increased and altered secretion of adipokines (TNF-α, adiponectin, leptin, etc.) directly to inflammation and insulin resistance; (2) ectopic fat deposition, predominantly in the liver, skeletal muscle, and β-cell, contribute to altered fat, insulin resistance, and glucose metabolism; and (3) mitochondrial dysfunction causing a bioenergetic cellular defect leading to decreased insulin sensitivity and defective pancreatic β-cell function.

Effects of Fetal Develop on Adult Glucose Metabolism

The Nurses' Health Study (NHS) of over 69,000 women found an inverse relationship between birth weight and adult diabetes [174]. A meta-analysis with an adjusted odds ratio of diabetes of 0.80, 95% CI 0.72–0.89 for each 1-kg increase in birth weight confirmed this [175]. However, a higher birth weight (>4.0 kg) is also associated with an increased risk of diabetes [176]. Lastly, a U-shaped relationship between birth weight and the development of T2D was found in a meta-analysis. Thus, high and low birth weight are associated with a similar increased risk of diabetes (ORs 1.36 and 1.47) [177] although not necessarily attributable to the same mechanisms.

The Effect of Adult Obesity on Glucose Metabolism

After absorption in the intestine and synthesis in the liver, triglycerides (TG) are transported in specialized lipoproteins (chylomicron and very-low-density lipoprotein (VLDL)) to adipose and other tissues. Intracellular toxic accumulation of diacylglycerol and the input and output flows of FFA and acyl-CoA can be ameliorated by the formation and safe storage as TG [178]. Droplets containing TG are surrounded by a monolayer of phospholipids and proteins, e.g., perilipin (ADRP), which regulates lipid droplet formation, growth, and dissolution [179].

Obesity and the Lipotoxicity Syndrome

The main function of the adipose tissue is fat storage. Adipose release of FAs and uptake into non-adipose tissues must be coupled, matching demand and supply. For instance, in fasted state or during physical exercise, the lipolysis in adipose tissue is increased, a process that requires the coordination of suppression of plasma insulin and elevation of contrainsulin hormones (glucagon, cortisol, epinephrine, etc.). However, in obesity it is quite normal to reach a prolonged overfeeding state, where fat load may exceed the functional storage capacity of the adipose tissue determining a state of metabolic inflexibility, where lipid uptake and mobilization is inefficient (inflexibility) (Fig. 14.4).

Another factor contributing to its functional defect is the adipocyte cell size. When adipocytes enlarge in an attempt to increase their capacity, they also become insulin resistant. This reduced the antilipolytic effect of insulin and increased the lipolysis of triglycerides from the adipose tissue as a whole and the bulk FFA release. This leak of FFA and accumulation in plasma subsequently promote insulin resistance in the muscle and liver [184] and also inhibits insulin secretion [185], ultimately causing β-cell apoptosis [186].

Among the most important factors controlling adipocyte capacity for storage and functional switch between storage and lipolysis, we identify the nuclear receptor PPAR-γ as a key transcription factor that controls the coupling between lipid storage and adipogenesis and lipolysis [187]. In addition, the direct role of leptin on adipose tissue functionality has been suggested. However, common forms of obesity are typically characterized by leptin resistance predominantly located at the central hypothalamic action [188]. Central and/or peripheral leptin action appears to be implicated in processes that prevent lipotoxicity in non-adipose tissues through the regulation of β-oxidation mediated in part by its effects through peroxisome proliferator-activated receptor-α (PPAR-α) activity. This prooxidative effect helps to minimize the metabolic burden of ectopic accumulation of lipids. Patients with insulin resistance syndrome have lower mRNA leptin abundance in peripheral adipocytes than IS patients (leptin resistance), even though insulin treatment acutely increases leptin levels [111, 189]. Another factor to consider is that a chronic increase of β-oxidation may contribute to oxidative stress and to generate inflammation, which may be potentially harmful [188].

Adiponectin, another adipose tissue-derived hormone, also has a major role in improving insulin sensitivity, anti-inflammatory, anti-apoptotic, and pro-angiogenic effects that enhance whole body and adipose metabolic flexibility. Adiponectin action in adipose tissue improves both the efficiency of the adipose tissue at regulating the releases of FFAs and increases the rate of FFA re-esterification during the postprandial state [190]. However, the low-serum adiponectin levels typically observed already in the early stages of insulin resistance are not sufficient to prevent the subsequent derail of adipose tissue function [111]. As part of the natural history toward the development of diabetes, there is progressive failure of the adipose tissue homeostatic mechanisms. When they are overwhelmed, lipids cannot hold efficiently in the adipose tissue and accumulate in tissues that

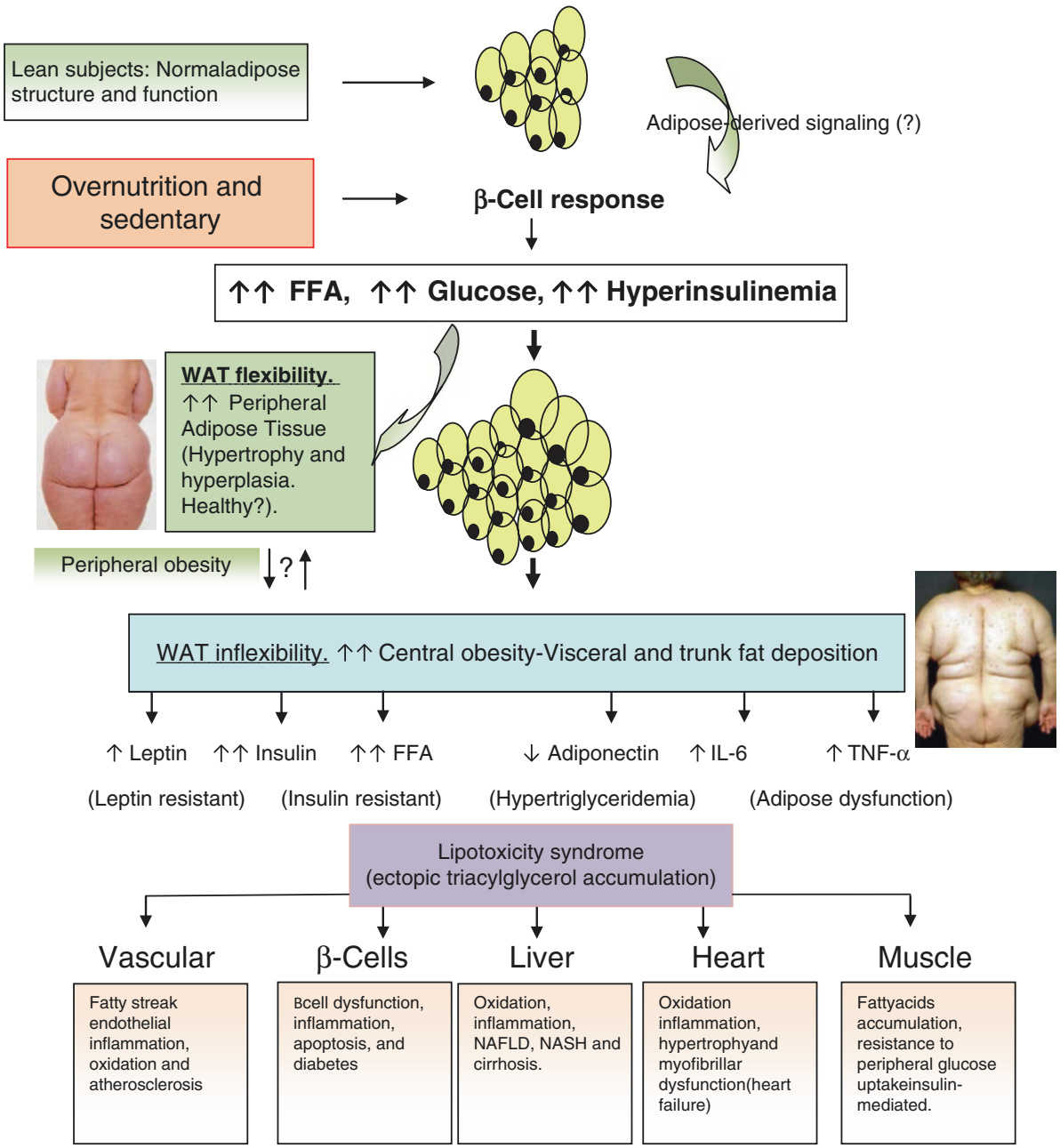

Fig. 14.4 Adipose tissue expandability and metabolic syndrome. After overeating with positive energy balance, adipose tissue increases its storage capacity, which is regulated by several factors. In individuals with a high capacity for storing fat, mainly when WAT is expanded (WAT flexibility), most, despite obesity developing, will remain normal, known as metabolically healthy obese (MHO). However, a low-grade chronic inflammatory response is frequently observed leading to dysfunctional adipose tissue [180]. Therefore, a proinflammatory milieu with elevation in IL-6 and mainly TNF-α, an altered adipokines profile with decreased adiponectin and increased leptin levels, will result in a dysfunctional adipose system. Increased release of cytokines and adipokines are related to insulin resistance, hyperglycemia, altered lipid profile, and cardiovascular diseases [111, 181, 182]. Insulin resistance is associated with the accumulation of lipids in non-adipose tissues such as the muscle (lipotoxicity), due to increased lipolysis of fatty acids from adipose tissue. On the other hand, when the maximal storage capacity of adipose tissue is achieve, dysfunctional adipose tissue results, and redistribution of fat is initiated. Limitation in fat storage capacity could be necessary and even precedes the development of metabolic factors. Ectopic lipid accumulation in non-adipocyte cells causes lipotoxicity in these organs, including inflammation and apoptosis. Thus, lipotoxicity in β-cells could decrease β-cell mass (β-cell dysfunction) and can cause diabetes. Increased fat in the liver leads to NAFLD and nonalcoholic steatohepatitis (NASH) and could cause hepatic dysfunction, myocardial dysfunction in the heart, the endothelial fatty streak could be a precursor of generalized arteriosclerosis, etc. The point at which adipose tissue begins to fail is probably influenced by genetic and epigenetic factors. However, the question is can storage capacity in WAT be enhanced to meet an increased demand [183]? One answer in humans is treatment with PPAR-γ agonists (TZDs) that transfer fat from central to peripheral deposits, improve lipid profile, insulin-sensitivity, and reduce diabetes and NAFLD [132]. *WAT* white adipose tissue, *MHO* metabolically healthy obese, *IL* interleukin, *TNF-α* tumor necrosis factor-α, *NAFLD* nonalcoholic fatty liver disease, *NASH* nonalcoholic steatohepatitis, *PPAR-γ* peroxisome proliferator-activated receptor-γ, *TZD* thiazolidinedione.

cannot store excess lipids such as the muscle, β-cells, liver, heart, and kidneys [124] without triggering metabolic toxic responses.

In addition with the leak of FAs, the dysfunctional adipose tissue also produces and releases an abnormal pattern of adipocytokine (e.g., decreased adiponectin and increased leptin, TNF-α, and IL-6). This promotes an inflammatory state that further compromises the insulin sensitivity and functionality of the adipose tissue depot. Advancing in the natural history, the development of central obesity further exacerbates hyperinsulinemia and hyperglycemia, initially in the postprandial state and finally to global hyperglycemia. This phenotype is typically associated with hypertriglyceridemia, hypoalphalipoproteinemia, hypertension, and fatty liver (dysfunctional metabolism in the liver), a cluster of pathologies commonly diagnosed as metabolic syndrome (MetS) [191].

Pathogenesis of Obese Type 2 Diabetes

Obese T2D is typically associated with four clinical and metabolic defects: obesity, insulin resistance, dysfunction of β-cells, and increased hepatic endogenous glucose production [192]. However, the mechanisms by which these defects progress, the way they affect each other and contribute to the increase of glucose levels in obese T2D, is not fully elucidated. In a landmark longitudinal study of obese subjects with high incidence of T2D (Pima Indians of Arizona), peripheral insulin effect (euglycemic clamp), acute insulin secretory response (AIR), and endogenous glucose production, in those whom glucose tolerance deteriorated from normal (NGT) to impaired (IGT) to T2D over 5.1 ± 1.4 years, were measured [192]. Patients who developed IGT typically presented increased body weight and decreased insulin sensitivity and defective acute insulin secretion. In those who developed an open T2D, a greater increase in body weight, coupled with a more severe insulin resistance and impairment of insulin secretion, and further increase of hepatic glucose production (HGP), was observed. By contrast, overweight patients who maintained normal glucose tolerance still gained weight despite decreased insulin-stimulated glucose disposal; however they maintained a robust insulin secretory response (AIR that was increased).

Another organ that is gaining relevance in metabolic failure associated with diabetes is the gut. The gastrointestinal tract should be considered as a large and specialized endocrine organ that releases two major incretin peptides. The glucagon-like 1 (GLP-1) by L-cells (distal small intestine) and glucose-dependent insulinotropic peptide (GIP) by k-cells (early small intestine). GLP-1 and GIP jointly contribute to rise by 60–70% insulin released in response to a mixed meal [193]. In the context of the obese T2D patients, their β-cells generate resistance to GLP-1 and GIP [194]. Thus, despite their levels being normal or minimally reduced, their signaling in beta-cells is dysfunctional. Moreover, GLP-1 also reduces glucagon releases by α-cells on the pancreas and reduces appetite. Finally, in these patients, the GLP-1 resistance results in hyperglucagonemia and increased HGP and contributes to weight gain by promoting an orexigenic response [195].

The kidney is another point of metabolic control [196]. The kidney generates about 15–20% of the endogenous glucose production, mainly in fasting period, and is controlled by insulin function. But the kidney in obese T2D is insulin resistant, leading to an increase in its glucose production. Furthermore, the glucose filtered is efficiently reabsorbed by sodium glucose transporter 2 (SGLT2) (80–90%) and SGLT1 (10–20%). During early stages of hyperglycemia, this capacity of reabsorption is increased and contributes to maintain elevated glucose levels but also to retain sodium and water which may contribute to increase high blood pressure.

Contributing to the phenotype, it could be argued that as insulin and amylin, which is released together with the insulin, have anorectic signaling properties acting in the hypothalamus, in obese T2D this signal of insulin is likely to be dysfunctional so that appetite is not suppressed which may contribute to overweight [197, 198].

Underlining Factors of Obesity-Induced Insulin-Resistance

Inflammation and Insulin Resistance

Long-time overfeeding and positive energy balance require adipocytes to increase their number and size. Excessive expansion of adipose is associated with adipose tissue metabolic dysfunction, changes in adipokines, increased hypoxia, immune cell infiltration, and attempts to remodel, cell death, and apoptosis. Inflammation is part of an early homeostatic response aimed to repair of damaged tissues (Figs. 14.3 and 14.4).

Enlargement of adipose tissue is associated with secretion by adipocytes of monocyte chemoattractant protein (MCP)-1, which promotes monocyte infiltration in WAT and differentiation in adipose tissue macrophages (ATM) [103]. Moreover, adipocytes also induce the expression of the adhesion molecules (ICAM-1) and platelet and endothelial cell adhesion molecule 1 (PECAM-1) on endothelial cells, which further attract monocytes [199]. The physiological role of this process is to facilitate the physiological remodeling of an expanding tissue. In obesity, failure to maintain the homeostasis of the organ results in uncontrolled inflammatory response generating a chronic low-grade inflammatory state. ATM contributes to the release of

inflammatory factors. Of relevance macrophages share many adipocyte genes such as fatty acid-binding protein 4 (FABP4) and PPARγ, whereas adipocytes can express numerous macrophage factors such as TNF-α, IL-6, and MMPs [200]. Moreover, ATMs have been artificially classified as M1 pro-inflammatory and M2 anti-inflammatory macrophages on the basis of membrane markers. In obesity typically there is an enrichment with a greater ratio of activated M1 than M2 macrophages [201, 202]. These proinflammatory M1 ATMs secrete pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, whereas M2 ATMs secrete anti-inflammatory cytokines including IL-10 and IL-1 receptor antagonist [202]. Of relevance the preferential type of ATM and degree of infiltration are linked with the progression of insulin resistance [203]. Hence, oversecretion of TNF-α from macrophages and to a lesser extent by adipocytes are a major characteristic of obesity and contributes to insulin resistance of obese humans (Fig. 14.3) [102, 109].

Inflammation of adipose tissue in obesity also involves infiltration of different T cells. Regulatory T cells (T_{reg}) represent 5–20% of the $CD4^+$ T cells and play a major role in controlling immune actions [204]. T_{reg} release anti-inflammatory cytokines, preventing macrophage infiltration and promoting an M2 macrophage phenotype [203]. Of relevance, with weight gain, a decrease in T_{regs} is observed [204], whereas there is an infiltration and activation of $CD8^+$ T cells that contribute to attract macrophages in the early stages of obesity [205].

Another relevant type of immune cells are the eosinophils, main contributors to IL-4-secretion, and represent about 4–5% of cells in WAT. Macrophages are the main target of IL4 promoting an anti-inflammatory M2 phenotype which can improve glucose metabolism through preservation of M2 macrophages in WAT [206]. Lastly, neutrophils also seem to participate in the immune cell infiltration of the AT, contributing to obesity-induced insulin resistance [207].

Insulin sensitivity is affected by inflammation through various mechanisms. **TNF-α** inhibits insulin action by altering insulin receptor substrate 1 (IRS-1), through the activation of its p55 receptor [208]. In addition, TNF-α, FFA, ROS, and hypoxia activate IκBα kinase β (IKKβ) and c-Jun N-terminal kinase 1 (JNK1) in WAT and the liver, inhibiting insulin activity by changing phosphorylation of IRS-1 [209, 210]. Furthermore, TNF-α also inhibits PPARγ function, impairing lipid synthesis and fat store in WAT. Moreover, inflammation increases plasma FFA levels through the stimulation of lipolysis and reduction of TG synthesis, inducing insulin resistance in adipose tissue [211].

IL-1β activity requires two stress response signals. The first, necessary for production of pro-IL-1β, needs the activation of TLR4 (LPS, SFA, etc.) [212]. The second, which converts pro-IL-1β to active IL-1β, is controlled by the NOD-like receptor (NLRP)3-caspase 1 inflammasome complex [213]. The formation of NLRP3 inflammasome is induced by stressors that include FFAs, glucose, adenosine triphosphate (ATP), uric acid, ROS, etc. [214]. Thus, activation of the NLRP3 induces caspase-1 activity that converts pro-IL-1β to mature IL-1β. The major roles of NLRP3 inflammasome and caspase-1 activity in obesity-induced IR have been recently described [215].

Interleukin-6 is secreted by the WAT, skeletal muscle, and liver [99, 216]. Plasma IL-6 levels increase in overweight patients [217] in response to high levels of insulin and TNF-α. IL-6 inhibits insulin action through phosphorylation of IRS-1 [218]. In addition, raised IL-6 plasma levels are also associated with steatohepatitis and liver dysfunction [216]. However, IL-6 appears to stimulate insulin secretion by increasing the number of GLP-1 receptors in β-cells [219]. Thus, increased IL6 may contribute to the early increase of insulin secretion observed in obese patients. In addition, while elevated IL-6 secretion from WAT and the liver appears to have adverse metabolic effects, increased IL6 secretion by the skeletal muscle seems to be metabolically advantageous. In fact, physical inactivity has been shown to reduce skeletal muscle IL-6 expression and secretion [220]. The difference may be that whereas the increase in plasma IL-6 levels induced by exercise results from glycogen/MAPK activation and activation of anti-inflammatory levels of IL-1RA and IL-10 levels [221], the IL6 secretion from adipose and liver is mediated by NF-κB—thus emphasizing the pleiotropic role of IL-6.

Finally, **interleukin-10** is an anti-inflammatory cytokine produced by monocytes, M2 ATMs, DCs, T cells, and B cells. Thus it is expected to play a favorable role in obesity-induced IR. Of relevance IL10 is decreased in T2D [222], whereas weight loss increases IL-10 expression in WAT concurrent with diminished pro-inflammatory gene expression [223].

Mitochondrial Dysfunction and Obesity-Induced Insulin Resistance

Mitochondria is the main site for oxidation of fatty acids and glucose; thus its dysfunction may contribute to FFA and lipid accumulation and favor IR [224]. Mitochondrial biogenesis is activated by insulin and diminished in subjects with IR [225, 226]. In humans the existence of mitochondrial dysfunction in obese T2D who display lower NADH:O_2 oxidoreductase activity and reduced mitochondrial size than lean subjects has been observed [227]. Moreover, mitochondrial dysfunction in obese and insulin-resistant patients decreases lipid metabolism in muscle compared with lean control subjects [227–229]. Therefore, when mitochondria is exposed to excess lipids for β-oxidation, the oxidation of glucose may

be impaired, contributing to a state of insulin resistance. Furthermore, mitochondrial function improves after exercise training, increasing uptake and oxidation of glucose in parallel with an improvement in insulin sensitivity [230]. In addition, molecular studies have found a decrease in peroxisome proliferator coactivator 1a (PGC1α), the key co-activator of mitochondrial biogenesis, and a decrease in phosphorylation pathways in muscle mitochondrial of T2D patients compared with control without diabetes [231, 232]. Thus, these studies have suggested the possibility of a genetic predisposition for mitochondrial dysfunction already observed in the early stages of insulin resistance and diabetes. Although a compensatory attempt to increase mitochondrial oxidative activity that could deal with the increased lipid supply in the short term has been shown [233], a sustained exposure to high-fat diet, prolonged for more than 4–6 weeks, may not be able to be compensated by increasing the mitochondrial activity leading to ectopic lipid accumulation and IR [234, 235]. However these observations are not consistently shown [236, 237]. It is still unclear whether the observed defects in mitochondrial function could be due primarily to a decrease in their number in muscle or secondary to metabolic defects within the mitochondria. It is known that insulin sensitivity improves after weight loss, an effect that does not require mitochondrial function to improve or even to change. Drugs which inhibit mitochondrial function and ATP production (TZDs, metformin, etc.) improve insulin sensitivity [238]. Lipid infusion-induced insulin resistance also enhances mitochondrial β-oxidation [239]. In non-obese sedentary humans after a period of overfeeding, IR was increased without changes in mitochondrial function [240]. Also muscle mitochondrial function was not distinctively impaired in obese and T2D compared with control subjects [240, 241]. Finally, there is some evidence that decreased mitochondrial function may induce insulin sensitivity, whereas an increase mitochondrial function is associated with insulin resistance in transgenic mice [236, 237]. Thus the relationship between mitochondrial and insulin action remains complex and still not well established.

Oxidative Stress and Obesity-Induced Insulin Resistance

The mitochondria are an important source of superoxide generation in cells, having the greatest capacity for production in the electron transport chain (ETC). Under physiological conditions, mitochondrial superoxide contributes to mitochondrial function. Several studies have proposed a relationship between oxidative stress and IR. Lipid infusion increased the levels of oxidative damage markers such as plasma thiobarbituric acid reactive substance (TBARS) and was associated with a decrease in insulin sensitivity [242]. A decrease in intracellular reduced glutathione (GSH) is associated with a decreased insulin sensitivity in T2D patients. In addition, the infusion of GSH improved oxidative damage and insulin sensitivity [242, 243]. However, the physiological contribution of ROS to insulin sensitivity and metabolic response remains controversial, and several studies have been unable to reproduce consistently these observations [244, 245].

Endoplasmic Reticulum Stress and Obesity-Induced Insulin Resistance

The endoplasmic reticulum (ER) is an important biosynthetic organelle that regulates many biological processes required for nutrient storage and metabolization. If the surplus of nutrients is greatly increased, the synthesis, processing, and secretion of proteins may need to be increased, generating ER stress and dysfunction. Accumulation of unfolded or misfolded proteins is observed with ER stress [246]. ER stress is also induced by factors such as hyperglycemia, viral infections, hypoxia, and lipid over load or qualitative changes in membrane lipid composition [246]. ER stress has also been linked to the activation of chronic inflammation by activating JNK [247], raised oxidative stress, insulin resistance [248], and leptin resistance in obesity [249]. Moreover, the amelioration of ER stress with drugs directly improves insulin sensitivity in obese mice and recently also observed in insulin-resistant obese patients [250]. However, the specific mechanisms and process by which ER stress induces insulin resistance in humans still remains to be fully elucidated.

Skeletal Muscle Glucose and Lipid Metabolism

Adiponectin exerts direct effects in the skeletal muscle where it promotes fatty acid oxidation, decreases intramuscular lipid accumulation, reduces toxic deposit of ceramides, and results in improved insulin sensitivity [67]. Leptin may also play an insulin-sensitizing role in the muscle through the CNS or through the leptin receptors which are highly expressed on muscle and participates on its growth. Leptin's effect seems more related to the enhancement in FFA oxidation and amelioration of lipid deposition in muscle mediated by AMPK activation [251].

Liver Insulin Resistance and Hyperglycemia

As the key organ regulator of lipid and glucose metabolism, the liver is commonly affected by ectopic lipid accumulation (Fig. 14.4). Fatty acids accumulation in the liver results from

the imbalance of different sources: dietary fat, increase in lipolysis from adipocytes, and from de novo hepatic lipogenesis, without excluding defects in oxidation and on lipoprotein assembly and secretion. High-fat diets have been shown to produce fatty liver, whereas low-fat/high-carbohydrate diets have been shown to produce hyperinsulinemia in the context of selective insulin resistance and stimulation of de novo lipogenesis via SREBP-1c. Thus, dietary composition can have a major effect by affecting the relative sources of fat in the liver. However, an overproduction of FFAs from adipose tissue in the context of obesity is probably the most likely source of the excess triglyceride accumulating in the liver [110].

When an inflammatory environment is established in the adipose tissue, the whole body lipid metabolism becomes altered, initiating postprandial hypertriglyceridemia, because the liver overproduction of VLDL is not removed in time and remains for longer in plasma (postprandial hyperlipidemia). Further, because lipolysis from peripheral adipose tissue is exacerbated, the interstitial content of FFAs increases, which can be taken up by the adjacent muscle cells (↓ IS) or again transferred into lipoproteins to the plasma and could be taken up by the liver (↑ VLDL production) and other organs (lipotoxicity).

The ectopic accumulation of fat in the liver has been strongly associated with both hepatic and adipose tissue insulin resistance, an almost universal finding in nonalcoholic fatty liver disease (NAFLD) [66, 252]. Thus, whereas insulin sensitivity is reduced by ~45–50% (whole glucose disposal), the ability of insulin to inhibit endogenous hepatic glucose production is also decreased. However, not all obese individuals necessarily develop metabolic complications, as some remain insulin sensitive and do not develop fatty liver [111].

On top of all these factors, the link between obesity and associated metabolic abnormalities seems to be better related to the topography, anatomical distribution, and/or the functional peculiarities of the adipose tissue, a phenomenon which seems to be more relevant in patients with relatively normal weight (Figs. 14.3 and 14.4). The mechanism(s) that increased visceral adiposity is associated with insulin resistance is unclear, but circulating hormones secreted from adipose tissue have been implicated in modulating insulin sensitivity. Importantly, adiponectin receptors (adipoR1 and AdipoR2) are expressed in the liver. Adiponectin is associated positively with insulin sensitivity and associated negatively with intraabdominal and hepatic fat. Adiponectin stimulates glucose use and fatty acid oxidation in the liver by activating AMP-activated protein kinase AMPK) and PPAR-α [67]. Moreover, adiponectin exerts a protective action on liver fat accumulation, favoring lipolysis by promoting the action of CPT-1 and enhancing fatty acid transport into the mitochondria to undergo β-oxidation, while preventing the action of FAS, ACO, and TNF-α and decreasing the expression and action of CD-36 protein that promotes the transport of fatty acids [112]. Adiponectin induces suppression of sterol response element-binding protein-1C (SREBPC-1), a key factor regulating lipogenic gene expression in the liver. In addition, adiponectin lowers toxic hepatic ceramide accumulation by enhancing ceramidase activity. Recently it has emerged that FGF21, released by adipose tissue, the liver, and the skeletal muscle, increases adiponectin levels. Also the treatment of T2D subjects with pioglitazone also increases adiponectin levels, and this has been associated with decreases in hepatic fat and correlated positively with hepatic and peripheral insulin sensitivity both pretreatment and posttreatment [253].

Leptin prevents de novo lipogenesis while activating β-oxidation of fatty acids in the liver and has anti-inflammatory effects on the liver. Leptin increases inclusion of triglycerides into VLDL enabling the release of lipid from the liver. Clinical trial are currently ongoing to show the effect of leptin therapy for NAFLD.

With respect to the role of the inflammatory cytokines IL-6 and TNF-α, the plasma levels of these two inflammatory cytokines are increased in subjects with NAFLD and NASH [111]. Moreover, the peripheral blood monocyte production of TNF-α and IL-6 is increased in subjects with NASH [254].

β-Cell Dysfunction in Obese T2D Subjects

In obese insulin-resistant subjects, the pancreatic β-cells homeostatically increase insulin secretion to maintain glucose levels. The mechanisms involved in this β-cell compensation are not well known, but result in both increased generation of β-cells and enhanced β-cell functional responses (Fig. 14.5) [259, 260]. β-cell mass is increased in obese compared with lean subjects [256]. The signaling for compensatory β-cell mass expansion may include increased glucose and FFAs (probably the most important direct stimulus), insulin, and other growth factors [259]. Glucose is the natural stimulus to release storage granules and to synthesize insulin by β-cells. Glucose must enter the β-cell by a special glucose transporter (GLUT2), increasing pyruvate and ATP/ADP ratio (glucose oxidation) which trigger insulin release (first phase) [261]. The maintenance of hyperglycemia stimulates specific β-cell glucokinase (GK) activity which forms 6-P-glucose that increases insulin production (second phase) [261]. The expression of GK and GLT2 are directly associated with the differentiation of β-cells, and both are regulated by PDX1 [262].

In addition, FFAs are essential for amplification of glucose-stimulated insulin secretion (GSIS), and other nutrient and non-nutrient stimulus [263]. First, the binding of FFAs

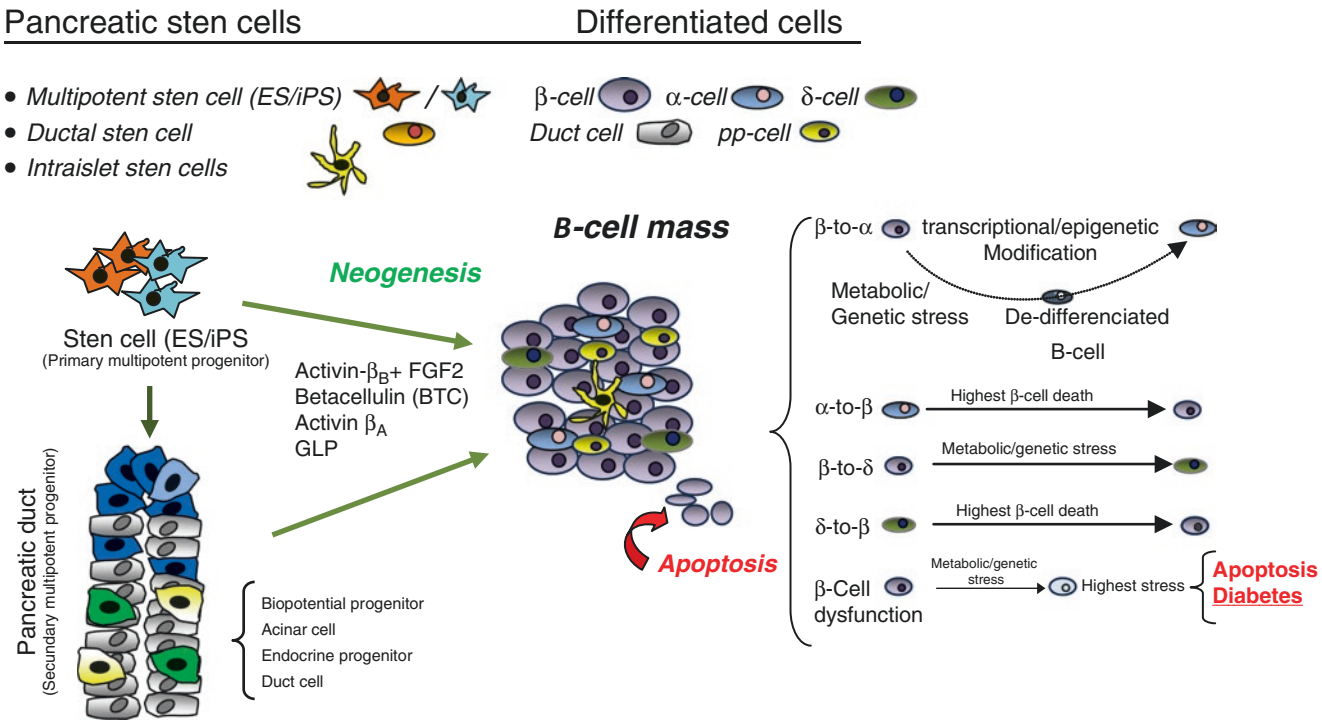

Fig. 14.5 Pancreatic β-cell failure appears as fundamental in the development of hyperglycemia in T2D, although insulin resistance may have been present for many years [255]. Insulin levels increase rapidly in relation with weight gain, probably associated with impaired insulin action; therefore hyperinsulinemia is frequently observed at diagnosis of T2D in obese subjects. However, only ~20% of obese subjects develop diabetes, while the remainder can maintain elevated insulin levels without hyperglycemia for many years. Thus, it appears that β-cell mass could progressively be reduced until it crosses a set point where insulin secretion is no longer sufficient to maintain the normal glycemic range in obese type 2 diabetic patients. Today, an increase in apoptosis of β-cells greater than a decrease in neogenesis is the most accepted cause for the loss of β-cell mass (Figure 14.5) [256]. β-cell death can be increased by an accumulation of high toxic lipids, a human islet amyloid polypeptide, and finally by the generation of high levels of glucose in the type 2 diabetes with obesity. In addition, in obese individuals, a high demand for insulin increases endoplasmic reticulum dysfunction (ER stress), and also hyperglycemia increases reactive oxygen species (oxidative stress)—both contributing to apoptosis of β-cells. Thus, if β-cell mass is lower than 50%, the remaining β-cells try to increase their function in order to compensate, which produces chronic β-cell stress. Therefore, proinsulin levels are frequently increased early in developing T2D, probably due to ER stress of β-cells. In addition, proinsulin levels after hemipancreatectomy determine the risk of developing diabetes, mainly in obese patients. Furthermore, the incretin effect is decreased in type 2 diabetes, affecting insulin secretion rates expressed as a percentage of insulin secretion. The incretin effect on total insulin secretion and β-cell glucose sensitivity and the GLP-1 response to oral glucose were significantly reduced in diabetes compared with NGT or IGT. Glucose tolerance and obesity inhibit the incretin effect independently [257]. In healthy subjects, infusion of physiological levels of GLP-1 increase insulin secretion. However, in patients with type 2 diabetes, physiological levels of GLP-1 had no effect on insulin release, whereas the infusion of GLP-1 at pharmacological levels (1 pmol/kg/min) increased just the "late-phase" (20–120 min) insulin response to levels similar to healthy subjects [258]. Furthermore, inflammatory pathways, such as increased interleukin-1β within islet β-cells, are involved in β-cell apoptosis in type 2 diabetes. Although the half-life and neogenesis rates of β-cells are difficult to establish in humans, it appears that β-cell can take several years to regenerate. However, interventions such as bariatric surgery can improve β-cell function in a few weeks in obese type 2 diabetes patients. In addition, β-cell function improved in obese T2D patients treated with a very-low-calorie diet (VLCD) weeks before insulin sensitivity was changed

to FFAR1/GPR40 receptors increases intracellular Ca^{2+} necessary for insulin release and second, through the generation of malonyl-CoA (inhibits fatty acid oxidation), which increases intracellular LC-CoA and diacylglycerol levels (DAG), in the malonyl-CoA/LC-CoA pathway [263, 264]. In addition, nutrients stimulate L-cells in the ileon, and higher fat content in food raises levels of glucagon-like peptide 1 (GLP-1) [265]. GLP-1 and FFAs can have synergistic actions, increasing GSIS [266], which may also stimulate β-cell growth [267, 268]. However, the incretin effect gets progressively impaired during the transition from IGT to diabetes. In addition, obesity and glucose tolerance each attenuate the incretin effect on β-cell function and GLP-1 response [257]. Pancreatic cells are connected with the parasympathetic system increasing insulin secretion, and its hyperactivity may be involved in the growth of β-cells [269]. Histological studies of the pancreas from necropsies and surgery have supplied important data for our knowledge of pathogenesis of islet β-cell dysfunction in T2D [256, 270]. An important research focused on the pancreas obtained from necropsies analyzed the total number of beta-cells (β-cell mass), the stage of beta-cell in regeneration and those

in apoptosis (Fig. 14.5). One hundred and twenty-four pancreases in total from lean and obese subjects were investigated, both groups having normal glucose tolerance and T2D and the obese group having the addition of impaired fasting glucose (IFG) [256]. In patients with normal glucose tolerance, the study found that relative cell volume was increased in obese versus lean cases ($P = 0.05$), increasing the mechanism of neogenesis ($P < 0.05$). However, a decrease of 40% and 63% in β-cell mass in IFG and T2D obese patients compared with obese normal glucose tolerance subject was also observed. Lean T2D patients compared with lean normal glucose tolerance subjects had a reduction of 59% in β-cell mass. The reduction of β-cell mass is evident in patients with impaired fasting glucose, suggesting that the loss of β-cell mass starts in the early stages. Finally, the study of mechanisms implicated in this loss of β-cell mass found no significant effect on β-cell neogenesis, but β-cell death by apoptosis was increased [256].

Underlying Mechanisms Implicated in β-Cell Failure in T2D

(a) **Glucotoxicity and glycation stress.** Insulin secretion is reduced during periods of hyperglycemia, while the partial recovery of β-cell function is achieved after the control of glucose levels in T2D patients. Glucotoxic mechanisms implicated in β-cell damage include increased glucosamine pathway activity and glycation stress, raised oxidative stress, increased ER stress, activation of inflammatory, and toxic accumulation of islet amyloid polypeptide (IAPP) [271, 272].

(b) **Mitochondrial dysfunction and reactive oxygen species.** Increased surplus of glucose and FFAs raises its oxidation in the mitochondria resulting in increased superoxide generation and production of uncoupling protein 2 (UCP2) in β-cell [273, 274].

(c) **Lipid effects on β-cell function.** An increased surplus of TG/FFA in β-cells induces glucose oxidation by which K+ATP channel pathway can be enhanced [266]. Thus, more than a direct lipotoxicity effect, elevated FFAs, and hyperlipidemia can be a major signal for a flexible adaptation of β-cell mass to obese-induced insulin resistance [266].However, the lipotoxicity effects of increased FFAs on β-cell can be seen more in combination with chronic hyperglycemia (glucolipotoxicity) [123, 264]. During hyperglycemia AMPK/malonyl-CoA signaling is stimulated, which slows down mitochondrial fat oxidation and promotes FFA accumulation in more complex lipids, some of which are lipotoxic [123, 264].

(d) **Islet β-cell exhaustion and ER stress.** The high requirements of insulin synthesis initiates mechanisms for compensating β-cell mass and generates high-endoplasmic-reticulum (ER) activity for the production of proinsulin. Continuous formation of proteins including insulin results in stress and dysfunction of the ER which affects the normal pattern of insulin secretion, a significant component of β-cell failure in T2D [275].

(e) **Differentiation of Undifferentiated Cells to Pancreatic β-cells.**

Hyperplasia, proliferation, and neogenesis of pancreatic β-cells may be adapted in relation to obese-induced insulin resistance and transitory β-cell damage. In humans pancreatic β-cell proliferation in pregnancy and T2D has not been observed. Therefore, similar to factors that induce multipotent stem cells (ES/iPS) to produce β-cells, we may be able to identify factors that inhibit pancreatic β-cell proliferation in various conditions. In humans, hyperglycemia progress is related with β-cell failure associated with a reduction of β-cell mass by increased apoptosis or dedifferentiation of β-cells during metabolic stressors such as is observed with obesity (Fig. 14.5).

Fate change between the different endocrine cells is observed under different conditions of stress. This may occur either directly or through a dedifferentiated state. Continued stress on the β-cell can lead to dedifferentiation that causes diabetes [276]. Future studies of some compounds that regulate endogenous stem cell differentiation could lead to drugs that stimulate β-cell neogenesis [277].

Multiple-Choice Questions

1. Talking about "Obesity, measurements, and assessment," which of the following statements is not correct?
   (a) Body mass index (BMI) is currently used to classify from low and normal weight to overweight and obese state in adults and is estimated by the weight/height squared ratio.
   (b) Deaths associated with a high BMI are ranked fourth behind deaths from hypertension, smoking, and unhealthy diets and ahead of deaths related to hyperglycemia, sedentary life style, high-salt intake, alcoholism, and high blood cholesterol level.
   (c) Several clinical parameters can be used to estimate central obesity, with the most widely being waist circumference (WC), hip ratio (HR), and waist-HR (WHR).
   (d) In research, to measure obesity and body fat distribution, more complex and more accurate techniques are used, such as dual energy X-ray absorptiometry

(DEXA), computed tomography (CT), and magnetic resonance imaging (MRI).

(e) **In research the single-voxel magnetic resonance spectroscopy is the gold standard for measuring distribution of body fat.**

2. With respect to the "Adipocyte and adiposity development," which of the following statements is not true?
   (a) In humans there are two types of well-differentiated adipose tissues, which have different distribution and functions, and are referred to as white adipose tissue (WAT) and brown adipose tissue (BAT).
   (b) The WAT is mainly related to the function of deposit of surplus energy as triacylglycerol, which could be mobilized and offered through hormonal signaling and has a tremendous ability to expand.
   (c) Adiponectin increases adipocyte lipid storage and prevents ectopic lipid accumulation. In addition, leptin decreases lipogenesis and increases lipolysis and fatty acid oxidation.
   (d) **Thermogenic function of BAT is mediated by the activation of a specific mitochondrial uncoupling protein 1 (UCP1), where the saturation of the production of ATP is dissipated as heat. Therefore, the activation of these sites with BAT decreases basal energy expenditure and increases onset of diabetes.**
   (e) The third fat cells, i.e., brown adipocytes, are also found infiltrating the skeletal muscle and in different areas of WAT. This could mean that the rate of lipid storage or lipid oxidation could be adapted and adjusted.
3. Which characteristics or pleiotropic effects of hormones and adipokines on adipogenesis and glucose metabolism is not correct?
   (a) Adipocyte differentiation and lipogenesis require insulin receptors and insulin action.
   (b) The infusion of hydrocortisone increases levels of circulating free fatty acids (FFA) associated with the activation mechanisms of lipolysis.
   (c) **The PPAR-γ agonists (thiazolidinediones, TZDs) increase central fat depots, decrease adiponectin levels, worsen lipid profile and insulin-sensitivity, and increase liver fat in NAFLD.**
   (d) Leptin is secreted by fat cells, establishing a negative feedback between the amount of adipose tissue and satiety centers in the brain.
   (e) Adiponectin is produced in mature adipocytes and is higher in peripheral adipose tissue than visceral adipose tissue.
4. Talking about inflammatory adipokines, all is true except for one.
   (a) Both TNF-α gene and its receptors are present in adipocytes and at higher levels in WAT. Increased release of TNF-α from adipose tissue may play a role in the impairment of insulin action.
   (b) **TNF-α increases the expression of PPAR-γ and increases the expression of genes involved in lipid and glucose uptake.**
   (c) A fatty acid-binding protein (aP2) could be the link between FFA and increased expression of TNF-α in obesity.
   (d) About one third of the total concentration of IL-6 is produced in adipose tissue, mainly in visceral adipose tissue compared with peripheral adipose tissue.
   (e) IL-6 levels are directly linked to obesity and insulin resistance and inhibit the activity of lipoprotein lipase (LPL).
5. Which of the "obesity effects on pathogenesis of type 2 diabetes" is not completely true?
   (a) Type 2 diabetes mellitus (T2D), at least at the beginning, is characterized by hyperglycemia, insulin resistance, and impairment in insulin secretion. The prevalence has increased as a result of obesity and sedentary lifestyle. But, can arise genetic or varying environmental factors, which complicates findings the cause in diabetic patients.
   (b) **The risk of T2D and cardiovascular disease rises not only with the amount of body fat and particularly increases when fat accumulation is in the peripheral depots.**
   (c) Increased and altered secretion of adipokines in obesity (TNF-α, adiponectin, leptin, etc.) contribute to insulin resistance.
   (d) Ectopic fat deposition, predominantly in the liver, skeletal muscle, and β-cell, contributes to altered fat and glucose metabolism.
   (e) Mitochondrial dysfunction and endoplasmic reticulum stress could be a link between obesity and diabetes, by decreasing insulin sensitivity and altering β-cell function.
6. In relation to "Obesity and Lipotoxicity Syndrome," all is true except for one statement.
   (a) Adipose tissue is the primary responsible for fat storage. Thus, a correctly functioning adipose tissue is necessary to maintain an adjusted delivery of surplus fuel to other tissues and nontoxic storage of lipids.
   (b) When the adipocytes enlarges, it develop insulin resistance; the antilipolytic effects of insulin is reduced. The increase of FFA in plasma results in more insulin resistance in the muscle and liver, inhibits insulin secretion, and induces β-cell apoptosis.

(c) **Leptin secretion decreases in parallel with fat accumulation, and as a result, the adipose tissue expands. Leptin action appears to be implicated in processes that increase lipotoxicity in non-adipose tissues.**
(d) Leptin regulates and increases β-oxidation through controlling peroxisome proliferator-activated receptor-α (PPAR-α) activity by minimizing ectopic accumulation of lipids.
(e) Adiponectin have a major role in improving insulin sensitivity, anti-inflammatory, anti-apoptotic, and pro-angiogenic effects that enhance the metabolic flexibility of adipose tissue.

7. In relation with "Pathogenesis of Obese Type 2 Diabetes," find out the statement that is not true.
(a) There are overweight subjects who maintain normal glucose tolerance. These can gain weight associated with insulin resistance (IR), but their acute insulin response (AIR) could be adjusted upward.
(b) The gastrointestinal tract is a large endocrine organ that releases two major incretin peptides. The glucagon-like 1 (GLP-1) by L-cells (distal small intestine) and glucose-dependent insulinotropic peptide (GIP) by k-cells (early small intestine) jointly rise by 60–70% insulin released in response to a mixed meal.
(c) GLP-1 reduces glucagon releases by α-cells on the pancreas and reduces appetite. In T2D patients the GLP-1 resistance results in hyperglucagonemia and increased HGP and weight gain by eating.
(d) **The kidney generates about a 15–20% of the endogenous glucose production, mainly in fasting period, and is controlled by insulin function. But the kidney in obese T2D is insulin resistant, and glucose production is decreased.**
(e) The glucose filtered is reabsorbed by sodium glucose transporter 2 (SGLT2) (80–90%) and SGLT1 (10–20%). When hyperglycemia is initiated, these capacity of reabsorption is increased and contributes to maintain elevated glucose levels and retention of sodium and water.

8. In relation with "β-cell dysfunction in obese T2D subjects," all are correct except one.
(a) In obese insulin-resistant subjects, pancreatic β-cells increases insulin secretion to maintain glucose levels. The mechanisms involved in this β-cell compensation are not well known, but implicate both increased generation of β-cells and enhanced β-cell responses.
(b) **The signaling for compensatory β-cell mass expansion includes increased glucose, while mainly FFAs, GLP-1, and insulin decrease β-cell mass, increasing apoptosis.**
(c) Glucose is the natural stimulus to release storage granules and to synthesize insulin by β-cells. Glucose must enter β-cell by a special glucose transporter (GLUT2) increasing pyruvate and ATP/ADP ratio (glucose oxidation) which trigger insulin release (first phase of insulin secretion).
(d) The maintenance of hyperglycemia stimulates specific β-cell glucokinase (GK) activity which forms 6-P-glucose that increases insulin production (second phase of insulin secretion).
(e) Pancreatic cells are connected by the parasympathetic system increasing insulin secretion, and its hyperactivity may be involved in the growth of β-cells.

9. Histological studies of the pancreas from necropsies and surgery have supplied important data for our knowledge of pathogenesis of islet β-cell dysfunction in T2D. Which of the following is not true?
(a) **In patients with normal glucose, tolerance has been found that relative cell volume is decreased in obese versus lean cases, decreasing the mechanism of neogenesis.**
(b) A decrease of 40 and 63% in β-cell mass in IFG and T2D obese patients compared with obese normal glucose tolerance subject has been also observed.
(c) Lean T2D patients compared with lean normal glucose tolerance subjects had a reduction of 59% in β-cell mass.
(d) The reduction of β-cell mass is evident in patients with impaired fasting glucose, suggesting that the loss of β-cell mass starts in the early stages.
(e) The study of mechanisms implicated in this loss of β-cell mass found no significant effect on β-cell neogenesis, but β-cell death by apoptosis was increased.

10. Talking about "the underlying mechanisms involved in the failure of β-cells in T2D," point out the incorrect one.
(a) Insulin secretion is reduced during periods of hyperglycemia, while partial recovery of β-cell function is achieved after the control of glucose levels in T2D patients (glucotoxic mechanisms).
(b) Glucotoxic mechanisms implicated in β-cell damage include increased glucosamine pathway activity and glycation stress, raised oxidative stress, increased ER stress, activation of inflammatory, and toxic accumulation of islet amyloid polypeptide (IAPP).
(c) An increased surplus of TG/FFA in β-cells induces glucose oxidation. Thus, more than a direct lipotoxicity effect, elevated FFAs, and hyperlipidemia can be a major signal for a flexible adaptation of β-cell mass to obese-induced insulin resistance.

(d) The lipotoxicity effects of increased FFAs on β-cell can be seen more in combination with chronic hyperglycemia (glucolipotoxicity).

(e) **Continuous formation of proteins, including insulin, results in stress and dysfunction of endoplasmic reticulum (ER) activity which does not affect the normal pattern of insulin secretion in T2D.**

11. The differentiation of undifferentiated cells to pancreatic β-cells plays a key role in the maintenance of the β-cell mass. Point out the incorrect of the following.

(a) Hyperplasia, proliferation, and neogenesis of pancreatic β-cells may be adapted in relation to obese-induced insulin resistance and transitory β-cell damage.

(b) In humans, hyperglycemia progress related with β-cell failure is associated with a reduction of β-cell mass by increased apoptosis and/or de-differentiation of β-cells during metabolic stressors such as is observed with obesity.

(c) Fate change of differentiation from multipotent stem cells (ES/iPS) between the different endocrine cells is observed under different conditions of stress.

(d) **Continued stress on the β-cell could lead to its dedifferentiation in α-cell, which will not affect the normal pattern of insulin secretion in T2D.**

(e) Future studies of some compounds that regulate endogenous stem cell differentiation could lead to drugs that stimulate β-cell neogenesis.

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Pathogenesis of Gestational Diabetes Mellitus

15

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Introduction

According to the American Diabetes Association (ADA), gestational diabetes mellitus (GDM) is defined as hyperglycemia diagnosed in the second or third trimester of pregnancy that was not overt diabetes before gestation. It constitutes the most common metabolic disease of pregnancy, with a continuously increasing prevalence [1, 2]. It has been associated with several maternal and fetal/neonatal complications [3, 4]. Increased maternal age; increased pre-pregnancy body mass index (BMI); excessive weight gain during pregnancy; Aboriginal Australia, Middle East, and pacific island ethnicity; positive family history of GDM; and higher parity are established risk factors for developing GDM [5, 6]. GDM, similarly to type 2 diabetes mellitus (T2DM), is a multifactorial disease; its pathogenetic mechanisms are not yet fully understood. Genetic predisposition and acquired factors (lifestyle and environmental) that affect insulin sensitivity and β-cell function have been implicated in GDM development and determine the disease severity [7]. Hormonal, inflammatory, and immunologic factors contribute to insulin production, secretion, and action, resulting in uncompensated insulin resistance and GDM development. Suboptimal lifestyles, such as hypercaloric diet, unhealthy nutritional habits, and reduced physical activity, contribute to central obesity and acquired triggering factors for GDM [8, 9].

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Insulin Sensitivity

Introduction

A major pathogenetic mechanism for GDM development is the reduced insulin sensitivity, called "insulin resistance," that progressively occurs in normal pregnancy. During the second half of gestation, the levels of placental and maternal hormones and pro-inflammatory cytokines increase in favor of fetal well-being and growth, thereby reducing maternal insulin sensitivity. In a healthy pregnancy, the expansion of the functional mass of β-cells compensates for the increased insulin demands resulting from the reduced insulin sensitivity. Insufficient β-cell compensation (see section "β-Cell Function and Insulin Secretion") or "excessive" decrease of insulin sensitivity results in GDM development.

Insulin action is impaired at hepatic, muscle, and adipose tissue levels in patients with GDM [10–12]. At the molecular level, insulin resistance is usually a failure of insulin signaling. Normally, insulin binding to insulin receptors causes phosphorylation of β-subunit of the receptor. It further leads to phosphorylation of insulin receptor substrate-I (IRS-I) at tyrosine residue, which acts as a docking site for other signal transduction molecules. Impaired post-receptor insulin signaling is mainly responsible for pregnancy-induced insulin resistance. Experimental studies showed impaired mRNA or protein expression of insulin signaling cascade components, such as insulin receptor substrate (IRS)-1 and IRS-2, a subunit of PI 3-kinase, as well as glucose transporter (GLUT)-1 and GLUT-4 in adipose tissue and muscle of women whose pregnancies were complicated by GDM. Decreased IRS-1 tyrosine phosphorylation, decreased GLUT-4 insulin-induced translocation to the cell surface, and decreased glucose transport into the cell were also found in muscle and adipose tissue of women with GDM [13–16]. Similar post-receptor insulin defects have been found in the placenta of GDM-affected pregnancies [17].

Chronic low-grade inflammation that characterizes obesity, which often accompanies GDM pregnancies, contrib-

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utes to insulin signaling impairment and aggravates "normal" gestational insulin resistance [18] and oxidative stress [19]. Alterations in the composition of the gut microbiome and its metabolites also seem to contribute to decreased insulin sensitivity and GDM development.

Placental Hormones

The placenta is a temporary fetal organ that forms the functional interface separating the maternal and fetal circulations and is important for mediating adaptations in maternal physiology. A plethora of hormones secreted by the placenta mediates maternal metabolic alterations to ensure fetal survival, growth, and well-being. They facilitate nutrient, gas, and waste exchange between the maternal and fetal circulations. Placental hormones, such as human placental lactogen (HPL) and placental growth hormone (GH), are opposed to insulin action [20]. HPL is a peptide hormone produced by syncytiotrophoblast and is gradually increased during pregnancy until about the 30th gestational week when it reaches a plateau. It acts mainly via prolactin (PRL) and, to a lesser extent, GH receptors on a wide variety of tissues. It is correlated to fetal weight and well-being as well as placental function [21]. HPL is the main insulin-resistance mediator during pregnancy. It acts as an "anti-insulin" agent to ensure adequate glucose supply to the embryo [22, 23]. HPL raises maternal blood glucose concentrations by increasing insulin resistance and raised free fatty acid concentrations by increasing lipolysis [24]. A sudden drop in HPL concentrations could indicate fetal distress [25–27]. Growth hormone (GH) is an anabolic hormone involved in carbohydrate and lipid metabolism; when in excess, it has diabetogenic properties, opposing insulin action [28]. Human placental GH is the main GH molecule produced during pregnancy, affecting maternal insulin sensitivity [29]. It is produced mainly by placental syncytiotrophoblastic cells and, similarly to HPL, acts mainly via prolactin (PRL) and, to a lesser extent, GH receptors. Opposite to maternal GH, its production and secretion are not regulated by growth hormone-releasing hormone (GH-RH) and is secreted tonically rather than in a pulsatile fashion. It is gradually increased by mid-pregnancy to term. Studies in transgenic mice showed severe insulin resistance induction by placental GH overexpression [30]. Maternal obesity and diabetes in pregnancy may be associated with a disrupted balance in the placental expression of HPL and GH [31]. Progesterone, produced initially by the corpus luteum and later by the placenta, is gradually increased during gestation and reaches many folds of pre-pregnant levels. It is known that progesterone inhibits insulin action in vivo and in vitro, mainly by inhibiting the PI3-kinase pathway of the insulin signaling cascade in the adipocytes [32]. It seems to have a central role in mediating the metabolic changes in pregnancy. Evidence about the association of GDM development and progesterone levels is scarce and conflicting.

Maternal Hormones

Maternal serum GH, other growth factors, such as insulin-like growth factor 1 (IGF-1), also called somatomedin, their binding proteins, prolactin (PRL), progesterone, and cortisol are altered in women whose pregnancies are complicated by GDM as compared to unaffected pregnant women [33, 34]. PRL is produced mainly by anterior pituitary lactotroph cells and, secondary, the central nervous system, immune cells, nonpregnant uterus, placenta, amnion, decidua, and the mammary gland. The most well-known action of PRL is lactation. Other PRL effects are mammary epithelial proliferation, corpus luteum function, and immune response [35, 36]. Evidence about PRL's effect on insulin sensitivity is contradictory. As in patients with a prolactinoma, hyperprolactinemia exacerbates insulin resistance to the nonpregnant state [37, 38]. The latter effect regresses after treatment with a dopaminergic receptor agonist [39]. On the contrary, studies in nonpregnant healthy women (with normal prolactin concentrations) showed that lower prolactin concentrations were correlated to decreased insulin sensitivity and increased risk for diabetes [40, 41]. During pregnancy, PRL is also produced by decidual cells and the fetal pituitary. Maternal PRL is increased gradually by conception to term [42]. In pregnant rats, increased prolactin concentrations have been correlated to a post-receptor insulin defect [20]. In humans, higher concentrations of PRL during the third trimester of pregnancy have been associated with decreased glucose tolerance, implying a causative relationship between hyperprolactinemia and GDM [43]. A recent case-control study of 321 women (107 GDM and 214 non GDM) showed a positive association between PRL levels in the first trimester of gestation and risk of GDM development [44]. On the contrary, in other studies, no difference in PRL concentrations has been found between GDM and controls [32, 45]. It has also been suggested that prolactin receptor gene polymorphisms are associated with gestational diabetes [46]. Maternal, placental, and fetal adrenal steroids; progesterone; cortisol; estrogen; and androgens also contribute to pregnancy-induced insulin resistance [47]. Cortisol can induce insulin resistance through post-receptor insulin defects [20]. Androgen receptors are overexpressed in placentas of GDM-affected pregnancies as compared to controls [48]. Although it is known that estrogens regulate carbohydrate metabolism, the underlying mechanisms are not fully understood. In the nonpregnant state, estradiol (E_2) partially affects insulin signaling by modifying mitochondrial function [49]. In GDM-affected pregnancies, estrogen

concentrations are lower as compared to unaffected pregnant women [50].

Maternal Vitamin D

Vitamin D is primarily known for its vital role in calcium homeostasis, skeletal mineralization, and bone metabolism. Besides this, vitamin D exhibits several extra-skeletal effects. Hypovitaminosis D, defined as low serum concentrations of 25-hydroxy-vitamin D3 ($25(OH)D_3$), has been correlated to many diseases, including metabolic diseases such as diabetes mellitus (T1 and T2DM). Some of its extra-skeletal properties regulate glucose metabolism, possibly through a beneficial effect on both β-cell function and insulin sensitivity. The mechanism of vitamin D effect on the latter is not yet fully understood. It seems to be achieved via different and possibly synergic processes such as indirect antioxidant and anti-inflammatory action, direct action on vitamin D receptor (VDR) expression, and insulin signaling through activation of peroxisome proliferator activator receptor (PPAR-) pathway and genomic action (control of epigenetic genes expression) of vitamin D. Several studies, though not all, have shown an association between low levels of vitamin D and T2DM development, in the nonpregnant state [51, 52]. Regarding GDM, current evidence shows a possible association between vitamin D blood levels and the risk of GDM [53]. However, heterogeneity across studies and contradictory results do not allow for safe conclusions to be drawn. Finally, a recent meta-analysis of 19 RCTs showed that vitamin D supplementation of women with GDM improved their glycemic control and indices of insulin resistance [54].

Maternal Adipokines

Maternal adipokines that are produced by her adipose tissue have a significant effect on insulin action. Their impaired secretion has been associated with several metabolic disorders, including insulin resistance, obesity, and DM2 in the nonpregnant state. It is suggested that adipokines may contribute directly and/or indirectly to metabolic dysregulation by enhancing chronic inflammation, aggravating insulin resistance, and resulting in impaired carbohydrate metabolism. Regarding pregnancy, it seems that impaired adipokines secretion may be associated with GDM development.

Adiponectin, an adipose tissue-derived plasma protein, has, in general, an anti-inflammatory action. It is produced mainly by white adipose tissue (WAT) in the nonpregnant state. It exerts pleiotropic effects through three receptors, AdipoR1, AdipoR2, and T-cadherin. Adiponectin seems to express protective properties for the vascular endothelium and the heart through anti-inflammatory action and suppression of the atherosclerotic processes [55–57]. It also has a beneficial effect on carbohydrate metabolism by increasing insulin sensitivity partially due to her main anti-inflammatory action [58, 59]. Higher concentrations of adiponectin have been associated with a lower risk of T2DM development in nonpregnant women [60]. In pregnancy, evidence about adiponectin concentrations is not consistent; all investigators have not confirmed placental production of adiponectin [61, 62]. Some studies have demonstrated increased adiponectin concentrations in early pregnancy and a gradual decrease after that compared to the pre-pregnancy state [63, 64]. In contrast, others suggest constant [65] or "normal" lower levels of adiponectin (hypoadiponectinemia) during pregnancy as compared to the nonpregnant state. Although evidence regarding gestational concentrations of adiponectin and carbohydrate metabolism is less clear, a link between hypoadiponectinemia and insulin resistance exists [64, 66], as pregnant women with GDM have lower adiponectin levels than healthy controls [65, 67].

Another adipokine, leptin, the most well-studied one, plays a central role in neuroendocrine signaling, homeostasis, and metabolism. It acts via hypothalamic leptin receptors and is strongly involved in metabolic issues affecting insulin secretion and action and tissue insulin sensitivity [68, 69]. Leptin is produced mainly by WAT adipocytes, proportionally to adipose tissue mass [70]. To a lesser degree, it is produced by brown adipose tissue (BAT), placenta, skeletal muscle cells, ovaries, and gastric cells. Leptin's primary action is the regulation of energy homeostasis [71]. In contrast to adiponectin, leptin has pro-inflammatory actions and, if in excess, exerts a deleterious effect on carbohydrate metabolism. It reduces insulin synthesis and secretion via negative feedback, whereas simultaneously increases tissue sensitivity to it [69, 72]. Obesity is associated with resistance to leptin action [73]. Its secretion is gradually increased during pregnancy, reaching a plateau, and is decreased before delivery. Placenta-derived leptin results in nearly a 100% increase in maternal serum concentrations [74, 75]. Further increased leptin concentrations have been found in GDM-affected women compared to non-affected pregnant women [76, 77]. Moreover, increased expression of leptin receptors has been found in the placenta of GDM-affected pregnancies [78]. Both adiponectin and leptin gene polymorphisms have been correlated to GDM occurrence [79]. Low adiponectin and high leptin concentrations during the first trimester may predict GDM occurrence during later pregnancy [80, 81].

Other adipokines such as fetuin B, visfatin, resistin, and apelin have been lately implicated in GDM pathogenesis. It is known that fetuin B impairs insulin action. Women with GDM-affected pregnancies have higher fetuin B concentrations as compared to controls [82]. Visfatin, or pre-B cell colony-enhancing factor (PBEF) or nicotinamide phosphoribosyltransferase (NAMPT), is produced mainly by the

human visceral adipose tissue. Though its action is not yet fully understood, it seems to get involved in energy homeostasis. It has been shown that visfatin elicits insulin-mimetic effects via binding to and activating insulin receptors in hepatocytes, myocytes, and adipocytes. Moreover, it increased insulin sensitivity in diabetic mice. During pregnancy, it is also produced by the human placenta, although to a lesser degree. Current results about the association of visfatin levels and GDM development are conflicting [83]. Resistin is a polypeptide secreted by adipose tissue in rodents and by macrophages in humans. It elicits pro-inflammatory activity and induces insulin resistance. A meta-analysis of 18 studies showed a positive association between maternal serum resistin levels and the risk of gestational diabetes mellitus [84, 85]. Data on apelin concentrations and their association with GDM are not consistent. Other novel adipokines, such as omentin and chemerin, have been associated with GDM development, and a causal effect is implied by some investigators [86].

Immunological Changes and Low-Grade Inflammation

Normal pregnancy is accompanied by immunological changes and a low-grade inflammation to the fetus's benefit [87, 88]. Inflammation is exacerbated by obesity, a common risk factor of GDM, and affects insulin sensitivity through post-receptor signaling defects. Inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), directly affect insulin action in healthy nonpregnant women, inducing insulin resistance [89]. TNF-α is a transmembrane protein produced mainly by activated macrophages in response to immunological stimulus [90]. To a lesser degree, it is expressed by other cells, such as lymphoid cells, cardiac myocytes, endothelial cells, and adipocytes. It expresses a cytotoxic effect on many cells; simultaneously, it regenerates tissues [91, 92]. TNF-α induces phosphorylation of the IRS-1, thus preventing the interaction of insulin with the insulin receptor and impairing insulin action. Interleukin-6 (IL-6) is a pro-inflammatory cytokine and an anti-inflammatory myokine expressed by immune cells, such as T cells and macrophages, visceral adipocytes, osteoblasts, and vascular smooth muscle cells. It is the main stimulator of the production of many acute-phase proteins. It impairs insulin-induced insulin receptor and IRS-1 phosphorylation, resulting in the inhibition of the insulin signaling cascade [93]. C-reactive protein (CRP) is an acute-phase protein of hepatic origin that is increased in response to inflammation and IL-6 secretion. It acts through activation of the complement system, triggering phagocytosis by immune cells. CRP is associated with insulin resistance in healthy individuals; high concentrations of high-sensitivity (hs)-CRP indicate a higher risk for metabolic, cardiovascular, and cerebrovascular disease [94]. The Generation R Study showed that increased CRP concentrations during early gestation are associated with a high risk of neonatal complications [95]. During normal pregnancy, low-grade inflammatory markers, such as CRP, IL-6, TNF-α, and GlycA, increase, suggesting an upregulation of systemic maternal inflammation [87, 96]. In contrast to this normal maternal adaptation, a further increase of some inflammatory markers is considered a risk factor for adverse pregnancy outcomes, including GDM. Specifically, it has been shown that women with GDM-affected pregnancies have increased IL-6 concentrations compared to controls [97]. In a recent meta-analysis, TNF-α is higher in GDM pregnancies compared to controls, independently of BMI [77]. CRP has been associated with GDM; an increase in its concentrations during early pregnancy is predictive of GDM development later in pregnancy [98, 99].

Oxidative Stress

Normal pregnancy is considered a condition of increased oxidative stress. Several pathologic conditions during pregnancy, including GDM, are associated with further aggravation of oxidative stress. It is believed that oxidative stress is caused either by increased reactive oxygen species (ROS) production or reduced antioxidant capacity [19]. Both increased oxidative stress markers and a decrease in antioxidative factors have been found in GDM-affected pregnancies. ROS induce an inflammatory response and inflammatory protein expression, aggravating the normal low-grade inflammation and insulin resistance during pregnancy. Furthermore, increased protein oxidation due to enhanced oxidative stress could be implicated in GDM pathogenesis [99, 100].

Maternal Gut Microbiome

Over the past few years, it has been increasingly indicated that alterations of the composition of the microorganisms colonizing the human gut, known as gut microbiome or microbiota, play a key role in developing metabolic disease. The gut microbiome has a pivotal role in regulating metabolic homeostasis. It is implied that a tripartite interaction between the intestine microbiome, immune system, and metabolism is a crucial participant in the pathogenesis of the metabolic disease, including type 2 diabetes mellitus (T2DM). It seems that an imbalance between commensal symbionts and pathobionts known as "gut dysbiosis" contributes to insulin resistance and chronic low-grade inflammation in T2DM patients. The production of metabolites during fermentation, activation of inflammatory cascades

leading to cytokine release, disruption of the permeability of the intestinal mucosal barrier, influx of toxins, and direct signaling action through incretin secretion are some of the implicated pathogenetic mechanisms [101]. Regarding GDM, although the impact of the microbiome on its development remains controversial, a growing body of evidence implies an association of gut microbiota dysbiosis to GDM. Alterations to microbial richness and composition, energy, and metabolic and transport pathways in the microbiome of GDM patients have been reported by some researchers. Because the diet is a powerful modulator of the gut microbiota, the latter represents a novel potential therapeutic target for GDM [102, 103].

β-Cell Function and Insulin Secretion

Introduction

The β-cell primary function is the production, storage, and secretion of insulin. β-cell dysfunction or failure can occur at any stage of the above processes, proinsulin synthesis, post-translational modifications, granule storage, sensing of blood glucose concentrations, and exocytosis of granules, resulting in hyperglycemia.

As mentioned above, during normal pregnancy, pancreatic cells adaptation occurs to compensate for the increased need for insulin. β-cell expansion and hyperfunctioning occur early in pregnancy to cope with the decreased insulin sensitivity after the second half of pregnancy [104]. Placental and maternal hormones, together with local regulators, like hepatocyte growth factor (HGF) and serotonin, work cooperatively to activate several signaling pathways, transcription factors, and epigenetic regulators to drive adaptations in β-cell mass and function during pregnancy. GDM is characterized by decreased insulin response to oral glucose and protein, sluggish first-phase insulin secretion, and delayed peak insulin secretion [105]. Subclinical pre-existing β-cell dysfunction and, to a lesser extent, a gradual decline of β-cell function during pregnancy due to the effect of maternal hormones and inflammatory mediators on its function constitutes the main mechanisms for the occurrence of GDM [106, 107]. Pre-existing β-cell dysfunction, due to genetic predisposition, does not allow for compensatory pancreatic β-cell hyperfunction to counter-regulate for the increased insulin resistance of pregnancy (Fig. 15.1) [108]. β-cell dysfunction in pregnancies complicated by GDM persists postpartum as compared to controls. Given the normalization of insulin sensitivity after delivery, only a small percentage of women with GDM remains within diabetic ranges; nevertheless, the risk for developing T2DM later in life remains increased (Fig. 15.2) [109]. An imbalance of hormonal and inflammatory factors, "glucotoxicity," "lipotoxicity," and oxidative stress have been associated with the aggravation of β-cell function and GDM development.

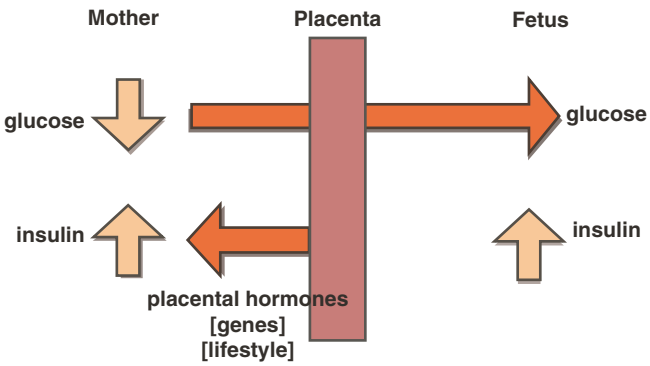

Fig. 15.1 Pathogenesis of GDM: the combination of maternal and placental hormonal alteration, genetic predisposition, and suboptimal lifestyle. (Adapted from: Poulakos P, et al. Comments on gestational diabetes mellitus: from pathophysiology to clinical practice. Hormones 2015;14:335–344)

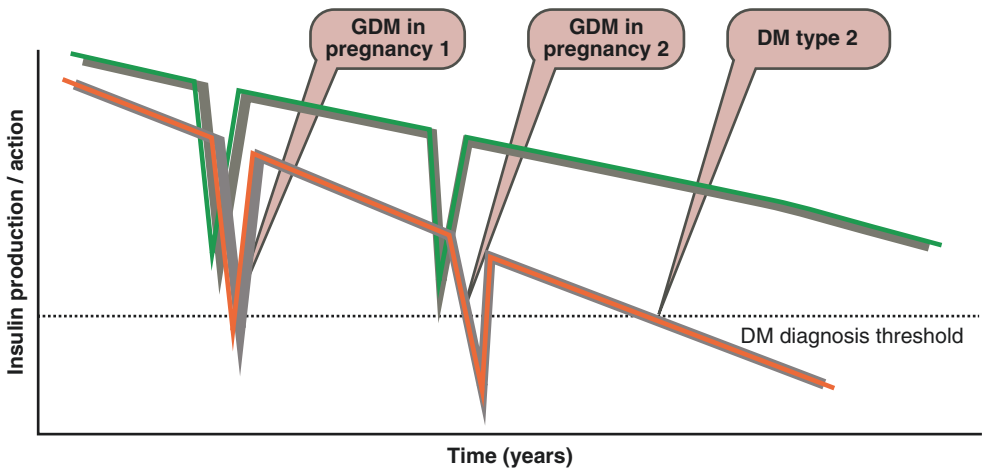

Fig. 15.2 T2DM development in women with prior GDM. Women with a history of GDM have an increased probability of developing GDM in later life due to genetic predisposition and suboptimal lifestyle. (Adapted from: Poulakos P, et al. Comments on gestational diabetes mellitus: from pathophysiology to clinical practice. Hormones 2015;14:335–344)

Maternal Hormones

The effect of maternal hormones on β-cell function and proliferation during pregnancy is still not completely understood. Although some results are contradictory, it is mainly suggested that they partially mediate β-cell proliferation, growth, neogenesis, insulin secretion, and apoptosis. Although PRL is considered a major regulator of β-cell expansion and hyperfunction during pregnancy, higher prolactin concentrations have been correlated to decreased glucose tolerance during late pregnancy [43, 110]. PRL receptor-null mice have shown β-cell maladaptation during pregnancy [111]. Moreover, PRL has been found to reduce menin concentrations, a known tumor suppression factor that suppresses β-cell proliferation and may be implicated in GDM development in pregnant mice [112]. 17β-estradiol seemed to be involved in β-cell adaptation and insulin secretion during pregnancy, specifically β-cell survival [113, 114]. Progesterone receptor-knockout mice have increased insulin secretion, probably due to increased β-cell mass [115]. The latter is in accordance with another experimental study that showed an apoptotic action of progesterone to pancreatic β-cells through an oxidative-stress-dependent mechanism [116]. Accumulating data have shown adipokines have a significant effect on β-cell function and survival. A leptin-induced decrease of insulin secretion by direct action on β-cells has been suggested. Moreover, leptin affects β-cell proliferation and apoptosis and inhibits insulin gene expression [117]. Another adipokine, adiponectin, seems to act directly on β-cell through its pancreatic receptors. It is known that adiponectin induces insulin release by β-cells through amplifying the exocytosis of insulin granules and increasing the insulin gene expression. Moreover, it reduces the rate of apoptosis in β-cells. Based on the evidence so far available, it is suggested that adipokines may have a crucial role in β-cell failure in the nonpregnant state [118]. Similarly, an imbalance of adipokines levels has been associated with GDM development [119].

Placental Hormones

Several hormones produced by the placenta have a key role in compensatory processes activated during gestation to maintain maternal euglycemia. It has been shown in animal studies that maternal β-cell compensation occurs before insulin resistance development and that the required β-cell expansion depends on secreted placental lactogens that signal through the prolactin receptors. Like maternal PRL, placental lactogens (PRL, PRL-like proteins, and HPL) seem to induce β-cell mass expansion by increasing β-cell proliferation and reducing their apoptosis in vivo and in vitro. Besides this adaptive increase in pancreatic β-cell mass, PRL and HPL also stimulate glucose-induced insulin secretion principally through upregulation of the glucose sensors [120]. Regarding GDM, polymorphisms or mutations in genes of the above hormones and their receptors have been reported in GDM-affected pregnancies. Other placenta-derived hormones, such as kisspeptin, are secreted into the maternal circulation, causing a significant increase in maternal blood concentrations, especially during the second and third trimester of pregnancy. Kisspeptin is a neuropeptide that in the nonpregnant state is most notably expressed in the hypothalamus and to a lesser extent in other areas such as pancreatic β-cells, liver adipose tissue, and brain. In addition to its known regulatory effect on human reproduction, novel peripheral roles for kisspeptin have been identified in metabolic pathways. Regarding GDM, low maternal concentrations of kisspeptin were observed in affected women [121].

Low-Grade Inflammation

As mentioned above, the low-grade inflammation that characterizes GDM affects glucose metabolism by increasing insulin resistance. Additionally, an impairment in adipokines production, possibly due to this inflammation, has also been correlated to β-cell dysfunction and decreased insulin secretion [77, 122]. Specifically, GDM-affected women have lower adiponectin concentrations as compared to controls [77, 123]. This hypoadiponectinemia of GDM pregnancy has been associated with β-cell dysfunction [124]. As part of the low-grade inflammation, GDM-affected women have increased TNF-α concentrations [77]. Beyond insulin resistance, TNF-α has a pro-apoptotic effect on β-cells [125]. The latter could contribute to the reduced insulin secretion of GDM. As mentioned above, GDM-affected women have lower concentrations of 25(OH)D_3. Vitamin D deficiency has also been associated with increased concentrations of inflammatory markers that could further deteriorate β-cell function [126].

Oxidative Stress

Beyond insulin resistance, oxidative stress per se or due to inflammation and hyperglycemia has been linked to decreased insulin secretion during the nonpregnant state [127]. GDM is characterized by increased oxidative stress as determined by increased concentrations of advanced glycosylated end products (AGEs) and other oxidative lipid and protein damage [100, 128]. Recently, a furan fatty acid metabolite, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF), has been recognized as a possible negative

regulator of β-cell function, inhibiting insulin synthesis and secretion through oxidative stress and mitochondrial dysfunction in human and mouse islets. Women with GDM have increased concentrations of CMPF as compared to controls [129]. Moreover, in GDM-affected women, CMPF predicted lower β-cell function indices [107].

Glucotoxicity and Lipotoxicity

The term "glucotoxicity" has been coined to describe the harmful effects of increased glucose levels per se on β-cell function and survival. "Glucotoxicity" is a well-known aggravating factor of β-cell function and autophagy. It is known that insulin resistance leads to hyperglycemia, and hyperglycemia itself reduces the insulin secretion capacity of pancreatic β-cells in T2DM patients. The latter vicious circle may finally lead to the total incapacity of β-cells to secrete insulin. Oxidative and endoplasmic reticulum stress and mitochondrial dysfunction seem to be the main pathogenetic mechanism of hyperglycemia-induced β-cell failure. Reduced mass, insulin secretion, and compromised identity of β-cell are the potential alterations induced by glucotoxicity [130]. Given that T2DM and GDM share common pathogenetic mechanisms, glucotoxicity could also be implicated in GDM pathogenesis.

The term "lipotoxicity" has been coined to describe the harmful effects of lipid accumulation, due to the chronic elevation of free fatty acids, in non-adipose tissues that result in cellular injury, dysfunction, and apoptosis [131]. β-cell is susceptible to elevated concentrations of blood lipids. Lipotoxic conditions have been shown to alter several processes of its main actions, insulin production and release, as well as the process of its autophagy. Similar to "glucotoxicity," the molecular mechanisms of lipotoxic β-cell dysfunction and apoptosis include oxidative and endoplasmic reticulum stress, mitochondrial dysfunction, impaired autophagy, and inflammation.

Accumulating evidence implicates lipotoxicity in T2DM pathogenesis through the latter effects on β-cell [132]. Regarding GDM, it has been associated with increases in maternal blood lipid levels [133], raising the possibility that, similarly to T2DM lipotoxic β-cell dysfunction, may be involved in its pathogenesis.

Maternal Vitamin D

As mentioned above, vitamin D exhibits several extraskeletal or pleiotropic actions. Moreover, it has been found that vitamin D has receptors in pancreatic cells and seems to prevent β-cell dysfunction or apoptosis partially via immunomodulatory action [51, 52]. Low vitamin D levels have been associated with β-cell dysfunction in the nonpregnant state; vitamin D supplementation has been shown to improve insulin secretion in rats [134, 135]. During pregnancy, several studies though not all have shown an association between lower vitamin D concentrations and GDM. Whether this association is causal remains, however, unclear. Moreover, lower vitamin D concentrations postpartum have been associated with impaired β-cell function in women with a history of GDM [136]. Increased parathyroid hormone (PTH) concentrations have also been implicated in GDM pathogenesis, partially through insulin secretion impairment [137].

Autoimmunity

A rare cause of GDM is autoimmune destruction of pancreatic β-cells, similar to type 1 diabetes mellitus (T1DM). Autoimmune GDM consists in less than 10% of cases. GDM-affected women with an autoimmune form of diabetes often develop T1DM soon after pregnancy or latent autoimmune diabetes of adulthood (LADA) some years after delivery [138]. In a Swedish population, antibodies implicated in T1DM pathogenesis (glutamic acid decarboxylase antibodies (GADA), islet cell antigen-2 antibodies (ICA)/tyrosine phosphatase antibodies (IA2)) have been detected in 6% of women with GDM [139]. Specifically, the prevalence of GADA in GDM-affected women has been shown to extend between 0 and 11%, of ICAs between 1 and 35%, of insulin autoantibodies (IAA) between 0 and 6%, and that of anti-IA2 between 0 and 6% [140]. Moreover, pancreatic autoantibodies may be developed in some GDM women postpartum [138]. GADA was positively associated with the postpartum development of diabetes in women diagnosed with GDM [141]. Consequently, positive GADA and other pancreatic autoantibodies in GDM-affected women can predict postpartum T1DM development [142]. A recent meta-analysis has shown an association between HLA class II variants, up to 30–50% of the pathogenesis of T1DM and GDM. Specifically, DQB1*02 and DRB1*1302 alleles have been significantly associated with an increased risk of developing GDM. On the contrary, DQB1*0602 seems to be a protective allele against GDM development [143]. HLA-DR6 alleles were also positively correlated to GDM development, whereas other haplotypes, such as HLA-DR2 and HLA-DR51, seem protective. Besides HLA-DR3 gene and HLA-DR6/DR9 heterozygote were associated with GDM severity and prognosis [144]. Other studies found no significant differences in HLA class II polymorphism distribution between GDM, impaired glucose tolerance (IGT), and unaffected pregnant women [145]. The evidence about the relationship between GDM and autoimmunity is still controversial, and more studies are needed to establish it.

Genetic Causes

Linkage and association studies, including GWAS, have implicated genetic and epigenetic mechanisms in GDM development. Polymorphisms and variants of factors such as transcription factor 7-like 2 (TCF7L2), hepatocyte nuclear factor 4α (HNF4a), glucokinase (GCK), and glucokinase regulatory protein (GCKR) genes may predispose to GDM development. Mutations of maturity-onset diabetes of the young (MODY) gene constitute rare causes of GDM. Several MODY gene mutations are present in GDM-affected women. MODY is an inherited form of diabetes resulting from a single, autosomal, dominant gene mutation that disrupts insulin secretion. It may be inherited to the offspring by both maternal and paternal origin; less frequently, it can be caused by de novo gene mutation. Nowadays, several types of MODY have been recognized. Genes that are implicated in MODY development are hepatocyte nuclear factor-1 homeobox a (*HNF1a*) gene that is responsible for MODY 3 development, glucokinase (*GCK*) gene for MODY 2, hepatocyte nuclear factor-4 homeobox a (HNF4a) gene for MODY 1, hepatocyte nuclear factor-1 homeobox b (HNF1b) gene that causes diabetes and renal cysts (MODY 5), insulin promoter factor (HPF1) gene for MODY 4, insulin gene for MODY 10, ABCC8 gene (sulfonylurea receptor-1 (SUR1) subunit) for MODY 12, potassium inwardly rectifying channel subfamily J member 11 (KCNJ11) gene for MODY 13, neurogenic differentiation-1 gene (NEUROD1) for MODY 6, kruppel-like factor 11 (KLF 11) gene for MODY 7, carboxyl ester lipase (CEL) gene for MODY 8, paired box-4 (*PAX4*) *gene for MODY 9*, and *BLK gene for MODY 11* [146–154]. These monogenic forms of diabetes constitute less than 10% of GDM; MODY 2 is the most frequent type associated with GDM [155]. Several other mutations of MODY genes have been detected in GDM women, such as HNF1a, IPF1, insulin gene, and KCNJ11 gene [156–160]. However, a causal relationship between MODY and GDM has not been established yet. Further investigation is needed regarding the possible clinical implications of MODY gene mutations on maternal and fetal health [155].

An impairment of the complex system of epigenetic mechanisms (DNA methylation, histone modification, a miRNA gene silencing) has been associated with T2DM and possibly GDM development. Several studies have shown that epigenetic changes in GDM-affected women precede the development of GDM and could constitute a risk factor of GDM, whereas other suggest that similar alterations are consequences of GDM [161].

Conclusions

GDM is the most common metabolic complication of pregnancy. Its prevalence has been increasing over the years and parallels the increasing obesity trend. The main pathogenetic mechanism is insulin resistance due to maternal and placental hormone alteration, maternal adipokine alteration, low-grade inflammation, and oxidative stress accompanying pregnancy and obesity. An additional pathogenetic mechanism is a β-cell dysfunction either pre-existing due to occult genetic predisposition or hormonal and inflammatory effects of pregnancy and obesity. It seems that several maternal and placental hormones act via different signaling cascades, transcription factors, and epigenetic regulators that modify receptor density, cell cycle-related genes, and the threshold for glucose-stimulated insulin secretion. Less frequent causes of GDM are autoimmune destruction of pancreatic β-cells (similarly to T1DM) and impaired insulin secretion caused by genes mutations, such as MODY).

Multiple-Choice Questions

1. Levels of placental and maternal hormones and inflammatory cytokines
   (a) Increase at the end of pregnancy
   (b) Are stable throughout gestation
   (c) **Increase in the first half of gestation**
   (d) Increase at the second half of gestation
   (e) Are decreased throughout gestation
2. Factors contributing to insulin signaling impairment
   (a) Obesity
   (b) Low-grade inflammation
   (c) Alterations of the gut microbiome
   (d) None of the above
   (e) **All of the above**
3. Placental hormones
   (a) Reinforce insulin action
   (b) **Are opposed to insulin action**
   (c) Are irrelevant to insulin action
   (d) Continue increasing throughout pregnancy
   (e) Have no systemic effect
4. The main insulin-resistance mediator during pregnancy
   (a) **Human placental lactogen**
   (b) Prolactin
   (c) Placental growth hormone
   (d) Adipose tissue
   (e) Fetal beta-cells

5. Gestational diabetes impairs
   (a) Progesterone levels
   (b) Insulin-like growth factor
   (c) Prolactin levels
   (d) A and B are correct
   (e) **All of the above**
6. Hyperprolactinemia:
   (a) Improves insulin sensitivity
   (b) **Decrease glucose tolerance**
   (c) Increase insulin levels
   (d) Decrease insulin levels
   (e) Increase fetal adrenal steroids
7. Maternal vitamin D
   (a) Has not effect on pregnancy
   (b) **Improves glycemic control in pregnancy**
   (c) Impairs glycemic control in pregnancy
   (d) Increases insulin resistance
   (e) Inactivates the PPAR-pathway
8. Adiponectin
   (a) **Has an anti-inflammatory action**
   (b) Impairs endothelial function
   (c) Reduces insulin sensitivity
   (d) Has a pro-inflammatory action
   (e) Has not effects on carbohydrate metabolism
9. Autoimmunity occurs
   (a) Rarely, in 1% of pregnancies with gestational diabetes
   (b) **In 10% of pregnancies with gestational diabetes**
   (c) In 20% of pregnancies with gestational diabetes
   (d) In 30% of pregnancies with gestational diabetes
   (e) Never occurs in pregnancy
10. Epigenetic mechanisms involved in gestational diabetes include
   (a) DNA methylation
   (b) Histone modification
   (c) miRNA gene silencing
   (d) **All of the above**
   (e) None of the above

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Nonalcoholic Fatty Liver in the Pathogenesis of Diabetes

16

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Introduction

Nonalcoholic fatty liver disease is prevalent worldwide, and currently, it is a major cause of chronic liver disease due to obesity-related epidemic, sedentary profile, and metabolic syndrome [1–3]. NAFLD presents with different phenotypes and may progress to cirrhosis and hepatocellular carcinoma. Moreover, it may be the leading cause for liver transplant in the next decade [4]. NAFLD was formerly identified in 1980, when Ludwig et al. described a small series of patients with liver histology characterized by fat accumulation, hepatic necroinflammation, and, in most cases, fibrosis, in the absence of a history of excessive alcohol consumption [5].

Definition of NAFLD

Currently, NAFLD is defined as the presence of macrovesicular steatosis in ≥5% of hepatocytes in individuals who consume little or no alcohol. NAFLD is divided into two major subtypes that comprises different phenotypes histologically identified: nonalcoholic fatty liver (NAFL, also termed simple steatosis), the nonprogressive form of NAFLD associated with increasing cardiovascular mortality that rarely develops into cirrhosis, and NASH, the progressive form of NAFLD that can lead to cirrhosis and hepatocellular carcinoma and is associated to an increase of liver-related mortality [6, 7]. NASH is characterized by the presence of steatosis, ballooning degeneration, and lobular inflammation, with or without perisinusoidal fibrosis on liver histology [8].

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In 2020, there was a consensus as a more appropriate name to describe fatty liver disease associated with metabolic dysfunction, ultimately suggesting that the old acronym nonalcoholic fatty liver disease (NAFLD) should be abandoned and replaced by Metabolic Non-Alcoholic Fatty Liver Disease (MAFLD). MAFLD might be defined based on the presence of liver steatosis plus some criteria linked to metabolic syndrome such as diabetes mellitus and obesity, among others [9]. Of note, the new nomenclature would not exclude other liver comorbidities like alcohol or viral hepatitis. However, this change is still under discussion [10, 11]. For this review, the name NAFLD will still be adopted.

Epidemiology

The rational for the high prevalence of NAFLD is multifactorial, being related to sedentarism, Western lifestyle worldwide, and obesity as well as to genetic and epigenetic factors. NAFLD is present in almost 30% of the general population [12]. The prevalence of NAFLD in Europe and the Middle East ranges from 20% to 30% [13]. In the USA, one-third of the population is obese, and one-third of American adults are thought to have NAFLD (Centers for Disease Control and Prevention *Overweight and Obesity* [online], http://www.cdc.gov/obesity/data/adult.html (2012)). NAFLD prevalence in Japan and China is similar to that in Europe (20–30% in Japan and 15–30% in China, respectively). In the Indian subcontinent, the prevalence of NAFLD in urban populations ranges from 16% to 32%; however, in rural India, where most people have traditional diets and lifestyles, the prevalence is around 9%, lower than in urban population [14]. In Latin America, the prevalence of NAFLD has been reported to range from 17% to 33% [15], but the increasing number of patients with type 2 diabetes mellitus is worrisome due to the association of these two diseases [16]. Data is lacking in the African continent; however, one study from Nigeria, which included patients with and without diabetes mellitus, identified a prevalence

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of 9.7% [17]. Is sub-Saharan Africa fatty liver disease related to metabolic diseases has emerged as an important burden of noncommunicable diseases [18]. Regarding pediatric population, the prevalence of NAFLD varies from 3% to 10%, rising up to 40%–70% among obese children [19]. Globally, NAFLD/NASH incidence increased from 19.34 million in 1990 to 29.49 million in 2017 among children and adolescents with an annual increase of 1.35% [20].

Patients with NAFLD and metabolic syndrome share the same risk factors like obesity, type 2 diabetes mellitus, dyslipidemia, and insulin resistance. Diabetes has a huge impact not only on its prevalence worldwide but also on NAFLD severity [21]. The prevalence of ultrasonographic NAFLD on a cohort of diabetic patients was described as 69.4%. Patients with NAFLD were more obese, had a higher waist circumference and serum triglyceride, and had higher alanine aminotransferase levels than those without steatosis [21].

Although cardiovascular death is the most common mortality-related cause among the NAFDL population, increasing data regarding liver-related death due to liver dysfunction and hepatocellular carcinoma [22] has been increasingly reported. Although HCC is usually diagnosed in patients with NAFLD-related cirrhosis, it has also been detected in non-cirrhotic NAFLD. However, its true incidence and risk is still unknown [22]. Compared to viral hepatitis, the progression of liver fibrosis in NAFLD seems to be slower (patients developing cirrhosis 28 to 57 years) [23]; however, the burden of patients with NAFLD is higher than those with hepatitis C [24]. At present, NASH cirrhosis is the third leading indication for liver transplantation in the USA [25]. In the forthcoming decades, due to a projected increase in HCC incidence, a change in the burden of related cases of HCC is expected, moving from viral hepatitis to NASH-related cirrhosis as the major risk factor for HCC worldwide [13].

Clinical Manifestations

The clinical presentation of NAFLD is humble. Most patients are generally asymptomatic at diagnosis and are often referred from an internist with an ultrasound that demonstrates steatosis. Indeed, abdominal ultrasonography, owing to its noninvasive profile and easy accessibility, is the main screening and diagnostic method for NAFLD [26], although it is limited for patients that have more than 33% steatosis on liver biopsy. Patients who are symptomatic usually have unspecific symptoms like fatigue and a dull pain or heaviness in the right hypochondrium. However, a physical exam with signs of insulin resistance like acanthosis nigricans an enlarged waist circumference (usually over 88 cm in women and 102 cm in men) and overweight should also be a clinical clue to the diagnosis of NAFLD [27]. It's also important to be aware of some clinical conditions that may be associated with insulin resistance like polycystic ovarian syndrome in young women, which usually presents with obesity, hirsutism, acanthosis, and other diseases like hypothyroidism, sleep apnea disease, and psoriasis which are closely related to an increased prevalence of NAFLD [28–30].

Diagnosis

Most patients with NAFLD are diagnosed by incidental elevated liver enzymes or imaging studies suggesting hepatic steatosis [31]. When NAFLD is suspected, the first step to confirm its diagnosis is to exclude other known etiologies of chronic liver diseases like drug-related steatosis [32, 33], viruses [34], and alcohol. As previously described, a careful history of alcohol ingestion and medications that are related to steatosis must be taken. Of note, some NAFLD patients with excessive alcohol intake may have both alcoholic and nonalcoholic fatty liver disease [35]. The average amount of alcohol that is allowed for patients with NAFLD have been under debate, but so far, although small to moderate amounts of alcohol might be related to a decrease in cardiovascular risk, patients with NAFLD should refrain from drinking alcohol [36]. Generally, for the diagnosis of NAFLD, the upper limit for alcohol intake would be a maximum of three drinks a day for men and two for women [31]. However, if we consider the definition of MAFLD, higher amount of alcohol intake did not need to be excluded [37]. Further studies are needed to better understand the outcomes related to this new definition regarding the composite of NAFLD and alcohol-related liver disease.

The different phenotypes of NAFLD are simple steatosis, steatohepatitis, and fibrosis. However, so far, due to the lack of specific and accurate biomarkers, only liver biopsy can accurately identify steatohepatitis. Steatosis is the most prevalent phenotype, and most patients with simple steatosis have a benign course of the disease. Although NAFLD is the most common diagnosis in patients with incidental abnormal liver function tests [38], laboratorial tests are of minor value since most patients with NAFLD including those with more advanced disease may present normal inflammatory liver enzymes, even those with type 2 diabetes mellitus [39]. However, patients with persistent abnormal liver enzymes are those who usually present NASH on liver biopsy or other liver comorbidities like viral or autoimmune hepatitis. In conclusion, routine AST/ALT do not differentiate steatosis and NASH or help staging liver fibrosis [40].

Liver Biopsy and Noninvasive Markers of Fibrosis

As already stated, the gold standard to accurately diagnose the different phenotypes of NAFLD is still a liver biopsy. However, it is an invasive method prone to inter-observer and intra-observer disagreement. In addition, it is painful and difficult to be performed in such a high burden and widespread disease. However, although all this drawbacks are well-known, liver biopsy is still required for inclusion of patients in clinical trials [41]. The search for accurate noninvasive methods to identify the different spectrum of the disease is still under research. So far, steatosis and fibrosis can be identified by noninvasive methods that vary from serological scores to image methods, and since the presence of fibrosis is the most important prognostic marker of the disease [42], it is reasonable to develop noninvasive methods that accurately identify or exclude liver fibrosis. At present there are a great number of serological scores that can be used to assess patients with NAFLD (Table 16.1). They are usually applied as screening tools mostly to exclude patients with higher risk for advanced fibrosis at primary care settings. McPherson et al. have compared FIB-4 with NAFLD-fibrosis score (NFS) (1.675 + 0.037 × age + 0.094 × BMI + 1.13 × IFG/diabetes + 0.99 × AST/ALT ratio − 0.013 × platelets − 0.66 × albumin), and there was also a high negative predictive value to exclude advanced fibrosis with the cut-off of −1.455 (NPV of 93%) [43].

The most recommended serological noninvasive test to exclude advanced fibrosis at primary care is FIB-4 [(age AST)/(platelets* Sqrt (ALT)]. A result <1.3 excludes advanced fibrosis with a high negative predictive value of 95%. Patients with FIB-4 higher than this should be reevaluated with an additional serological marker like enhanced liver fibrosis (ELF) or an imaging noninvasive method such as vibration-controlled transient elastography (VCTE). FIB-4 followed by the evaluation of liver stiffness by VCTE or ELF test in those with indeterminate values (FIB-4 between 1.3 and 2.67) maintained an acceptable performance while reducing the rate of indeterminate results [44]. The ELF panel consists of the following three extracellular matrix turnover proteins: hyaluronic acid, tissue inhibitor of metalloproteinase 1, and N-terminal pro-collagen III-peptide. When used, ELF panel has had excellent performance to exclude advanced fibrosis in a low fibrosis prevalence setting like primary care. For a fixed sensitivity of 0.90, the best cut-off was 7.7 with a low specificity (34%) and a PPV of 7–26% but an excellent NPV of 95–99%. In a high prevalence fibrosis setting (above 30%), ELF can lead to a 75% PPV for a threshold of 10.51 [45].

If the patient has a FIB-4 less than 1.3 and a VCTE elastography less than 8 kPa or an ELF test <7.7, he might be kept in primary care and advised for lifestyle modification, assessment of cardiovascular risk, and serial measurement of noninvasive tests [46, 47].

NASH is the phenotype of NAFLD that points to a progressive form of the disease, and currently only liver biopsy is able to make this diagnosis. The histological definition of NASH comprises the triad of steatosis, cell injury (ballooning), or any amount of lobular or portal inflammation [48]. Of note, fibrosis is not required for the diagnosis of NASH. Semiquantitative histological scoring systems have been proposed for NAFLD, but they are not useful in clinical practice, and each has certain limitations. Recently, Bedossa et al. developed a new histological classification for NAFLD: the FLIP algorithm and the SAF (steatosis, activity, fibrosis) assesses separately the grade of steatosis, the grade of activity, and the stage of fibrosis. This algorithm and score may improve the agreement between pathologists when describing fibrosis stage [48]. However, the most used histological classification for NAFLD is still the NASH Clinical Research Network that considers the NAFLD activity score, NAS, that punctuates steatosis (0–3), ballooning (0–2), and lobular inflammation (0–2) and a separate classification for fibrosis (0–4). A NAS score of 5–8 is considered diagnostic for NASH, while a NAS of 3–4 is considered borderline [49].

Other noninvasive tools that have been useful as screening methods for the identification of patients with higher risk of fibrosis are VCTE, two-dimensional shear wave elastography (2D-SWE), acoustic radiation force impulse (ARFI), and magnetic resonance with elastography (MRE). Although MRE has been considered the most accurate method for the identification of liver fibrosis, its use is limited as screening method [50].

VCTE uses an ultrasound displacement M-mode and A-mode image produced by the system. It has two probes, M and XL. The XL probe was designed for obese patients, which has increased the success rate of the exam in patients with NAFLD since most are obese, and before the development of the XL probe, most exams were unreliable. Currently, all patients with a skin-to-liver capsule distance (SCD) of

Table 16.1 Diagnostic performance of serologic scores to evaluate fibrosis in NAFLD

Test	AUC	Cut-off	Se (%)	Sp (%)	PPV (%)	NPV (%)
NFS	0.81 (0.71–0.91)	−1.45	78	58	30	92
		0.676	33	98	79	86
FIB-4	0.86 (0.78–0.94)	1.30	85	65	36	95
		2.67	26	98	75	85
ELF[a]		7.7	93	34	26	95
ELF[b]		10.51	51	93	75	81

NAFLD nonalcoholic fatty liver disease, *NFS* NAFLD fibrosis score, *Se* sensitivity, *Sp* specificity, *NPV* negative predictive value, *PPV* positive predictive value

[a] Fibrosis prevalence <20%

[b] Fibrosis prevalence >30%

>25 mm should be assessed with the XL probe [51]. TE results under 7.9 kPa have a high negative predictive value for advanced fibrosis (97%) and should be employed in daily practice to decide about performing a liver biopsy in patients with NAFLD [52].

Two-dimensional shear wave elastography (2D-SWE) evaluation needs to be performed in a well-visualized area of the right liver lobe, without the visualization of large vessels, liver capsule, ligaments, and the gallbladder [53]. Obesity, which is one of the most prevalent findings in NAFLD patients, might limit a successful exam in addition to poor acoustic window or presence of artefacts and inability of the subjects to hold their breath [54].

In a study that compared the diagnostic performances of supersonic shear imaging (SWE) for the diagnosis of liver fibrosis compared to ARFI and TE in chronic liver disease, SWE, TE, and ARFI correlated significantly with histological fibrosis score; AUROCs of SWE, TE, and ARFI were 0.89, 0.86, and 0.84 for the diagnosis of mild fibrosis; 0.88, 0.84, and 0.81 for the diagnosis of significant fibrosis; 0.93, 0.87, and 0.89, for the diagnosis of severe fibrosis; and 0.93, 0.90, and 0.90 for the diagnosis of cirrhosis, respectively. Hence, all methods might be used to assess liver fibrosis in patients with NAFLD, since the reliability criteria are respected as well as its limitations [54]. Additional studies with 2D-SWE and ARFI are needed in order to better establish the best cut-offs for these methods.

NAFLD and T2DM Interplay

In order to better understand the interplay between NAFLD and T2DM, it is important to review epidemiological data and pathogenetic mechanisms accounting for this relationship.

As discussed before, T2DM is a risk factor for NAFLD and its progressive forms, NASH and advanced liver fibrosis [39, 55]. Interestingly, in addition to T2DM, a family history of diabetes was independently associated with NAFLD risk and with the presence of NASH and fibrosis in NAFLD patients [56, 57].

In our cross-sectional study, no diabetes-related variable (glycemic control, diabetes duration or the presence of long-term complications) was associated with the more severe stages of NAFLD [21]. In contrast, data are emerging to suggest that the presence and severity of NAFLD may be associated with the occurrence of macro- and microvascular complications in diabetic patients [7, 58, 59]. Some mechanisms could explain those epidemiological observations. Chronic hyperglycemia may promote or aggravate NAFLD in the same way it induces micro- and macrovascular diabetic complications. It accelerates the production of advanced glycosylation end ,products (AGEs) and interferes with the hepatocyte microenvironment, activating Kupffer and hepatic stellate cells (both have receptors for AGE) [60].

It has been demonstrated that over 85% of subjects with NAFLD have impaired glucose tolerance or T2DM by standard oral glucose tolerance test (OGTT) [61, 62]. Therefore, another issue to be considered is whether NAFLD is an important precondition for the development of T2DM. In this regard, several studies have shown an increased incidence of T2DM in patients with NAFLD diagnosed by ultrasonography or only by elevated liver enzymes. However, most of them were conducted in Asian countries, and few were properly adjusted for potential confounding variables [63, 64]. In a prospective cohort study of 3153 participants from the Multi-Ethnic Study of Atherosclerosis, high liver fat was independently associated with development of T2DM [65]. Two systematic reviews with different criteria for selecting studies of NAFLD patients obtained similar results. The two independent reviews demonstrated an increased risk for incident diabetes over a period of 4–10 years [66, 67]. Recently, Mantovani et al. performed a meta-analysis of relevant studies and concluded that NAFLD is significantly associated with a twofold-increased risk of incident diabetes [68]. Taken together, these observations have implied a role for NAFLD in T2DM pathogenesis.

Pathogenetic Mechanisms

During the course of human evolution, individuals who had more energy stores were more likely to cope with starvation. In modern industrialized societies, with unlimited access to caloric food, this evolutionary adaptation becomes maladaptive. An increased caloric intake exceeding rates of caloric expenditure promotes obesity, dysfunction of white adipose tissue, and accumulation of ectopic lipids. This relationship between the nutritional oversupply and NAFLD is reflected by the high prevalence of NAFLD and insulin resistance (IR) among obese individuals.

Metabolic Mechanisms Involved in NAFLD

Adipose Expansion and Inflammation

As obesity and the deposition of ectopic fat increase, adipose tissue is more likely to be infiltrated with macrophages and undergo inflammation. In fact, it is the tissue-specific distribution of fat from adipose tissue into ectopic depots and not the whole-body quantity of fat that determines insulin resistance. Visceral adiposity is known to be highly active in releasing adipocytokines that are implicated in NAFLD development. It has been demonstrated that VAT (visceral adipose tissue) has been associated with hepatic steatosis,

insulin resistance, and dyslipidemia because of its higher lipolytic rates [69]. Another hypothesis is that VAT was not a primary cause of NAFLD, but just a marker for an abnormal adipose tissue distribution related to a lower subcutaneous mass [70].

The expanded and dysfunctional adipose tissue triggers inflammation through recruitment and retention of macrophages and secretion of inflammatory cytokines such as tumor necrosis factor α (TNFα) and interleukin 6 (IL-6). TNFα activates pro-inflammatory pathways: the nuclear factor κB (NF-κB) and c-Jun N-terminal kinase (JNK) [71]. These pathways, via activation of various kinases, increase even more the release of inflammatory cytokines, modulate adipocyte transcription factors, and attenuate insulin signaling. TNFα-induced attenuation of insulin signaling is mediated by JNK and occurs via serine phosphorylation of insulin receptor substrate [72]. Adipokines provide an important link between adipose tissue and insulin resistance. Serum levels of adiponectin, a hepatoprotective adipokine, are reduced in patients with NAFLD, metabolic syndrome, and T2DM [73]. Adiponectin improves insulin sensitivity and decreases both steatosis and inflammation [74] and is inversely related to NAFLD development and progression [75]. All these adipose inflammatory events contribute to a systemic inflammatory and insulin-resistant state that predisposes to T2DM.

Insulin Resistance and Hyperinsulinemia

There is strong evidence of the association of NAFLD and insulin resistance (IR). Euglycemic hyperinsulinemic clamp studies, coupled with tracers infusion confirmed that the IR is the rule in main tissues even in nondiabetic and non-obese patients with NAFLD [76]. Insulin is a pleiotropic hormone that regulates different cell functions. Concerning lipid metabolism, insulin promotes triglyceride storage and inhibits lipoprotein lipase activity in adipose tissue. Insulin resistance at the level of the adipocyte seems to be the primary defect in NAFLD [77]. Impairment in insulin-mediated suppression of lipolysis leads first to elevated circulating non-esterified fatty acids (NEFAs) and subsequently to a sustained excess delivery of these fatty acids to the skeletal muscle and liver. In fact, there is growing evidence that chronically elevated plasma NEFAs concentrations can lead to insulin resistance in muscle and liver and impair insulin secretion by pancreatic beta-islet cells.

Adverse effects on the metabolism of carbohydrates are dependent on increased endogenous glucose production and reduction in peripheral glucose uptake. Chronic hyperglycemia induces insulin secretion by the pancreatic beta-islet cells, leading to compensatory hyperinsulinemia. The mechanisms of beta cell progressive failure are less well defined; however elevated levels of glucose and increased circulating NEFAs may be responsible for pancreatic beta-islet cells dysfunction and apoptosis [78]. The processes of beta-cell deterioration in response to elevated glucose and NEFAs levels are traditionally known as "glucotoxicity" and "lipotoxicity." Thus, with prolonged nutrients' toxicity, as metabolic capacity of beta-cells is overwhelmed, insulin production declines. It is the progressive loss of beta-cell insulin secretion in the setting of insulin resistance (IR)/hyperinsulinemia that leads to the development of T2DM.

Metabolic Consequences of NAFLD

Hepatic Lipogenesis and Hypertriglyceridemia

Interestingly, it has been argued that many of the adverse effects due to insulin resistance result much more from compensatory hyperinsulinemia in organs that remain sensitive to its action. In fact, there is selective insulin resistance even in different pathways within the same tissue or organ. In the liver, for instance, while insulin fails to suppress gluconeogenesis and to activate glycogenesis, it continues to promote FAs synthesis (de novo lipogenesis—DNL). The major direct effect of insulin on endogenous glucose production is the regulation of glycogen synthesis. With development of hepatic insulin resistance, insulin no longer stimulates glycogen synthase, and therefore glucose is redirected into lipogenic pathways, resulting in NAFLD and hypertriglyceridemia [79]. Insulin also regulates adipose tissue lipolysis and influences the amount of NEFAs for hepatic fatty acid esterification, independent of its hepatic action.

Hyperglycemia and compensatory hyperinsulinemia activate transcription factors sterol regulatory element-binding protein-1c (SREBP-1c) and carbohydrate response element-binding protein (ChREBP), which upregulate most genes involved in DNL [80].

The production of long-chain FAs is determined by the sequential action of various enzymes: acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), and fatty acid elongases and desaturases [81]. In turn, the key regulator SREBP-1c directly controls many of these enzymes and liver × receptor, which is also an important component of the nuclear receptor superfamily.

Hence, the action of these upregulated lipogenic enzymes and the increased delivery and uptake of FAs (adipose tissue and diet) play a critical role in the induction of NAFLD. Hepatic steatosis develops when the balance between hepatic triglycerides (TAGs) synthesis from free fatty acids (FAs) exceeds the liver capacity to oxidize FAs or export TG in the form of very-low-density lipoprotein (VLDL). FAs may be oxidized in the mitochondria, peroxisomes, and microsomal system. β-oxidation within mitochondria, however, is the most efficient source of energy

under normal circumstances. Patients with NAFLD/NASH can have impaired uptake and oxidation of FAs by mitochondria in the liver and throughout the body in other tissues [82, 83]. Fatty acid esterification into hepatic triglycerides results in increased VLDL production and hypertriglyceridemia present in most patients with NAFLD and T2DM. Defects in triglyceride export, as reduction in production of apolipoprotein B, can lead to liver steatosis but with extremely low VLDL and triglycerides levels [84].

Hepatic Insulin Resistance and Hyperglycemia

Although hepatic TAGs are thought to be inert or even protective for NAFLD progression, FAs metabolites such as diacylglycerol (DAG) may further contribute to IR and NASH development. The causal link between plasma membrane DAG-specific stereoisomers and IR is attributed to PKCε activation. Activated PKCε isoform binds and inhibits insulin receptor kinase, leading to reductions in insulin-stimulated tyrosine phosphorylation of insulin receptor substrate IRS-2 and insulin signaling [85]. In contrast to DAG, there was no consistent association between other lipid mediators, such as ceramides, and hepatic insulin resistance [86]. The selective insulin resistance (IR) in the liver is a key pathophysiologic event in the development of NAFLD and type 2 diabetes. Differences in insulin receptor (InsR) activation underlie the selective IR of glucose production relative to lipogenesis. Decreased (InsR) activation has been observed in the liver of patients with NAFLD and results from a cell-autonomous downregulation of receptor number and/or activity in response to chronic hyperinsulinemia. It has been shown that a greater degree of intact InsR signaling is required to suppress glucose production than to stimulate lipogenesis, one through Forkhead O transcription factor-1 (FOXO1) and the other through SREBP-1c [87]. These "bifurcation" of hepatocyte insulin signaling underlies the mechanisms by which one branch (i.e., glucose metabolism) becomes resistant to the effects of insulin, whereas the other (i.e., lipid metabolism) remains sensitive, or even stimulated by hyperinsulinemia. These molecular features of hepatocyte insulin signaling do not rule out the role of plasma membrane DAGs as the key cellular compartment and lipid species in hepatic IR. Recent data have shown that this is also the mechanism behind the insulin resistance in adipose tissue and skeletal muscle [88, 89].

Other Mechanisms Involved in NAFLD Pathogenesis

Genetics Factors

During last years, genome-wide association studies revealed a growing list of genetic variants associated with NAFLD pathogenesis. Patatin-like phospholipase domain-containing protein 3 (PNPLA3), transmembrane 6 superfamily 2 (TM6SF2), membrane-bound *O*-acyltransferase domain-containing 7 gene (MBOAT7), and glucokinase regulator (GCKR) single-nucleotide polymorphisms (SNPs) were validated in large and independent cohorts. The most well-described genetic risk variant is the I148M variant in PNPLA3 gene. The I148M allele leads to a loss of phospholipase lipolytic activity, which predisposes to increased hepatic fat content and progressive liver damage. In addition, I148M variant confers an increased risk of fibrosis progression and hepatocarcinoma in NAFLD patients. In the case of TM6SF2, (Lys E167K) T allele has been associated with hepatic retention of TAG and hepatic fibrosis and (Glu E167K) C allele with VLDL secretion and atherogenesis. However, both genetic variants in PNPLA3 and TM6SF2 have not been associated with IR or increased risk of T2DM [90, 91].

MBOAT7 rs641738 T allele was shown to increase the risk of the entire spectrum of NAFLD through changes in the phospholipid acyl chain remodeling [92].

The P446L variant in GCKR gene increases glucose uptake and DNL in hepatocytes. In this setting, hepatic lipid accumulation from constant glucose substrate favors liver disease but protects from T2DM development.

Recently, a new protective SNP was discovered. HSD17B13 (rs72613567:TA) gene variant is associated with loss of retinol dehydrogenase activity in hepatocytes. Interestingly, the presence of this loss of function variant seems to attenuate the risk liver injury of I148M allele in PNPLA3 gene [93].

Diet and Gut Microbiome

High-calorie diets and sedentary lifestyle have been linked to many pathological conditions including metabolic syndrome, type 2 diabetes mellitus, and NAFLD. In addition to the amount of calories, dietary composition may also contribute to NAFLD development. Recent data have suggested that increased consumption of fructose and sugar-sweetened beverages, saturated fatty acids (SFAs), and high trans-fat-containing ultra-processed food can have a dismal effect on the development and progression of NAFLD.

More emphasis is being placed on fructose consumption on NAFLD pathogenesis. Fructose can enhance liver steatosis via de novo lipogenesis—DNL through activation of SREBP1c, independently of insulin [94]. Fructose also inhibits fatty acids oxidation, reducing the action of PPARα - FGF21 hormone axis [95]. Moreover, fructose inhibits leptin expression, decreasing satiety [96]. Finally, fructose interferes with gut microbiota composition, increasing intestinal permeability, and endotoxinemia, which also promotes IR [97].

It is difficult to differentiate the effects of poor dietary habits and gut microbiome function and composition on NAFLD pathogenesis since they are both closely linked to obesity and its comorbidities. Patients with NAFLD have an altered gut microbiota composition and increased intestinal permeability, allowing LPSs and other products to enter the portal circulation. These observations have implied an important role for gut microbiota-induced inflammation in the development of NAFLD and insulin resistance [98, 99]. Toll-like receptors TLRs are a family of receptors that plays a critical role in innate immune systems. TLR4 received a particular attention because of its ability to recognize free fatty acids and lipopolysaccharides (LPSs) and activate the proinflammatory signaling pathway nuclear factor κB (NFκB). Thus, LPSs have an indirect effect on insulin sensitivity and inflammation [100, 101].

Gut microbiota may also contribute to NAFLD by increased production of branched-chain and aromatic amino acids, phenylacetic acid, ethanol, and short-chain fatty acids. Taken together, those gut metabolites increase nutrient absorption, fat accumulation, and generation of reactive oxygen species (ROS) and hepatic inflammation, leading to NAFLD progression [102–104].

Mechanisms Involved in NAFLD Progression

NAFLD progression results from a cascade of cellular and signaling events between hepatocytes, macrophages and other immune cells, and hepatic stellate cells. Metabolic mechanisms and other factors (genetic, diet, and gut microbiome) involved in NAFLD pathogenesis may influence the propensity for cell injury and liberation of proinflammatory and fibrogenic signals. Hepatocellular injury in NASH is characterized by activation of nuclear receptors, altered insulin signaling, mitochondrial dysfunction, enhanced endoplasmic reticulum stress, lipogenesis, and lipotoxicity [105]. Hepatocyte injury is a cornerstone of progressive NASH since it serves as a trigger for increasing inflammation and fibrosis [106].

Soluble and extracellular vesicles signals from hepatocytes lead to proinflammatory activation of macrophages and other immune cells. Activated macrophages release cytokines and chemokines which further contributes to hepatocyte apoptosis and recruitment of immune cells into the liver. Hepatic stellate cells are activated by stressed or apoptotic hepatocytes and by inflammatory and immune cells. Activation of stellate cells results in increasing extracellular matrix production and fibrogenesis [107].

The current concept is that not all patients with NASH share, in the same intensity, the same mediators and signaling pathways to develop inflammation and fibrosis. Future knowledge of different pathways will open up new diagnostic strategies and therapeutic interventions.

Multiple-Choice Questions

1. Among the options below, mark the one that contains the findings that must be present in liver biopsy in order to make the diagnostic of steatohepatitis.
   (a) Steatosis, fibrosis, and lobular inflammation
   (b) Fibrosis, ballooning and steatosis
   (c) Steatosis, ballooning, and lobular inflammation
   (d) Fibrosis, ballooning, and portal inflammation
   Correct answer: (c)
2. Patients with NAFLD usually have metabolic syndrome. Mark the option that includes other risk factors for NAFLD.
   (a) Polycystic ovarian syndrome
   (b) Graves' disease
   (c) Chronic hepatitis B
   (d) Gaucher disease
   Correct answer: (a)
3. Patients with cirrhosis have an increased risk of hepatocellular carcinoma. Mark the correct sentence.
   (a) In NASH, hepatocellular carcinoma may develop without cirrhosis.
   (b) Currently it is recommended to screen patients with diabetes for hepatocellular carcinoma.
   (c) Pioglitazone is associated with a higher risk of hepatocellular carcinoma in NASH patients.
   (d) Metformin should be quit in diabetic patients with NASH due to the risk of hepatotoxicity.
   Correct answer: (a)
4. The noninvasive method for the detection of fibrosis that has the best accuracy in patients with NAFLD is
   (a) Transient hepatic elastography
   (b) APRI
   (c) BARD
   (d) The combination of FIB-4 and elastography
   Correct answer: (d)
5. Mark the correct sentence regarding NASH.
   (a) NASH may be diagnosed in patients with a NAFLD score >0.675.
   (b) So far the only way to diagnose NASH is by performing a liver biopsy.
   (c) Metformin is linked to improvement of NASH.
   (d) In order to improve NASH, patients should lose 5% of their body weight.
   Correct answer: (b)

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Part III

Examples of Global Experiences in Diabetes Care

Diabetes Management in Asia

17

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Diabetes Burdens in Asia: Morbidity and Mortality

Asia is considered as the epicenter of the global diabetes epidemic [1]. The major implications to the existing diabetes burden in Asia are the rising burden of young-onset diabetes mellitus and a higher risk of diabetes complications [2, 3]. According to the 10th edition of IDF Diabetes Atlas 2021, 1 in 11 adults in Southeast Asia (SEA) and 1 in 8 adults in the western pacific (WP) are living with diabetes. Further, one in two adults living with diabetes is undiagnosed, thus contributing to increased risk of micro- and macrovascular diabetes complications [4]. The proportion of all-cause deaths attributable to diabetes is 14.1% in SEA region and 11% in WP region [5]. Asia region has one of the highest age-standardized disability-adjusted life years (DALYs) associated with diabetes mellitus [6]. Figure 17.1 shows the global trend in the age-standardized DALYs attributed to diabetes by World Bank regions between 1990 and 2019. Both East-Asia and Pacific and South Asia regions have experienced a sharp increase in the diabetes-related DALYs over the last two decades.

Early-onset diabetes among children and adolescents is now emerging as a major public health concern in Asia. An interplay of higher rates of central obesity, insulin resistance, and genetic predisposition is implicated to contribute to rising burden of young-onset diabetes among Asians. In addition to this, conventional risk factors like smoking, alcohol, and diets rich in sugars, lack of physical activity among the middle class and rural populations has also contributed to the increase in the diabetes burdens in Asia [7]. Figure 17.2 shows the relative contribution of metabolic, behavioral, dietary risk factors, tobacco, and air pollution. Compared to other regions, air pollution has emerged as a novel risk factor contributing to the diabetes DALYs burden in Asia.

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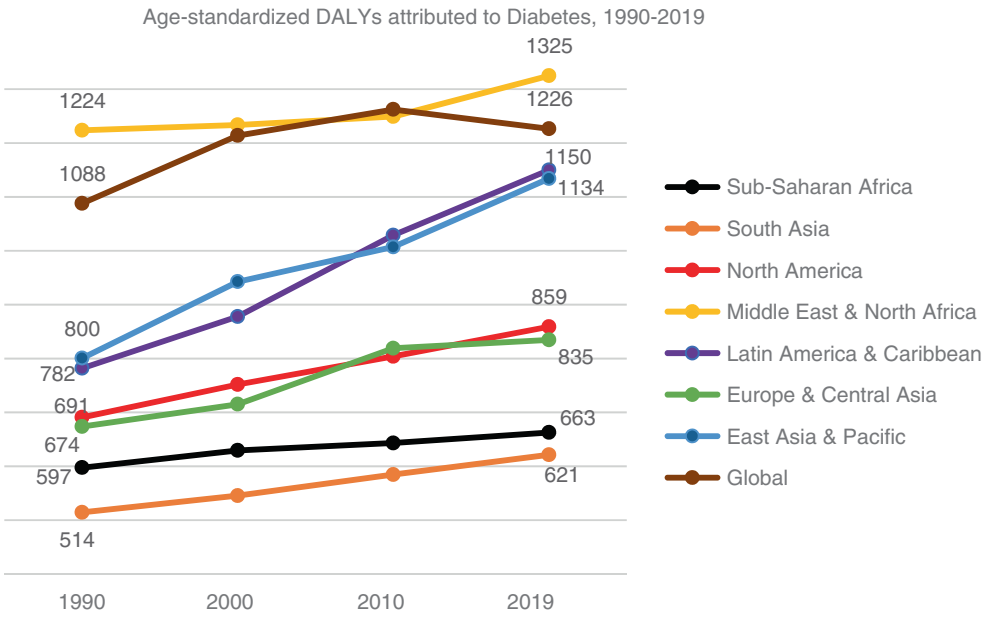

Fig. 17.1 Age-standardized DALYs attributed to diabetes between 1990 and 2019. (Source: Using data from the Global Burden of Disease Study 2019 database. https://vizhub.healthdata.org/gbd-compare/)

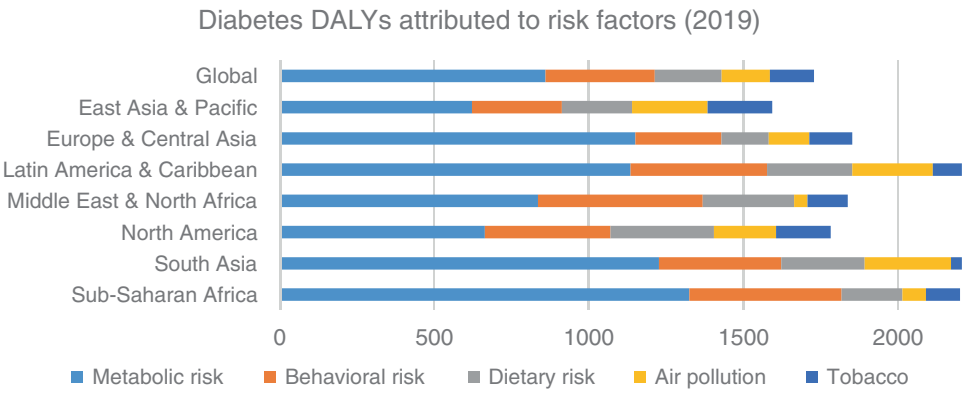

Fig. 17.2 Diabetes DALYs attributed to risk factors, 2019. (Source: Using data from the Global Burden of Disease Study 2019 database. https://vizhub.healthdata.org/gbd-compare/)

Prevalence and Incidence of Diabetes and Related Complications

The top-ranked countries in 2019 with the largest number of adults with diabetes were Asian countries including China (116.4 million) and India (77 million). Also, recent data suggest an increasing prevalence of type 1 diabetes in Asia region with a prevalence of 9.6 per 10,000 and incidence of 15 per 100,000 [8]. Further, a study from India reported the secular trends over 10 years and found that the prevalence of diabetes increased from 18.6% to 21.9% in cities, 16.4% to 20.3% in towns, and 9.2% to 13.4% in peri-urban villages. Abdominal obesity was significantly associated with the increased trend in diabetes prevalence, even among the villagers [9]. Another 2018 study by Geldsetzer et al. analyzed National Family Health Survey (NFHS-3) dataset to determine the prevalence of diabetes and hypertension in India and its variation by state, rural vs. urban location, and individual-level sociodemographic characteristics found that diabetes prevalence was highest in the middle and old age across all geographical areas and sociodemographic groups in India [10].

In 2019, global estimates for the number of incident cases of type 1 diabetes in children and adolescents aged 0–14 years were ~98,200 and ~128,900 for aged 0–19 years. India with 15.9 thousand cases ranked first for the estimated number of incident cases of type 1 diabetes in children and adolescents (0–14 years) per annum. The prevalence of diabetes complications among people with diabetes in select Asian countries is shown in Table 17.1. The prevalence of diabetic neuropathy appears to be significantly higher in Sri Lanka (63%) and Indonesia (59%) compared to other countries in Asia.

Table 17.1 Prevalence of diabetes complications in people with diabetes in select Asian countries

Country (year), (source)	Diabetic retinopathy (%)	Diabetic neuropathy (%)	Diabetic nephropathy (%)	Diabetic foot	Amputation	CHD	Stroke
China (2019) [11]	8.1	11.1	20.7	NA	NA	NA	NA
Sri Lanka (2018) [12]	26.1	62.6	50.8	2.6%	1.3%	10.6%	1.1%
Vietnam (2020) [13]	11.6	37.9	24.1	6.3%	0.9%	33.4%	4.4%
Indonesia (2019) [14]	29.1	59.1	14.5	12.4%	NA	22.8%	4.6%
India (2018) [15]	19.2	16.8	11.2	10.4%	2.4%	21.2%	5.6%
India (2021) [16]	27.5[a]	10.4	29	NA	NA	NA	NA

[a] Type 2 diabetes. *CHD* coronary heart disease, *NA* not available

Table 17.2 Diabetes prevalence, undetected rates, and mean expenditure per person in Asia

Country	20–79 population (in 1000s)	Diabetes prevalence estimates (%)	Undetected/total diabetes estimates (%)	Mean expenditure per person with diabetes in USD
Afghanistan	1090.8	6.4	73.4	167.5
Bangladesh	8372.2	8.1	56.0	63.9
China	116,446.9	10.9	56.0	936.2
India	77,005.6	8.9	57.0	91.6
Indonesia	10,681.4	6.2	73.7	365.2
Iran	5387.2	9.4	34.8	1141.1
Iraq	1505.0	7.6	47.1	555.5
Japan	7390.5	7.9	46.6	3178.9
Jordan	544.2	9.9	45.9	712.5
Malaysia	3652.6	16.8	50.4	980.4
Nepal	696.9	4.0	69.5	80.4
Pakistan	19,369.8	17.1	43.8	83.3
Philippines	3993.3	6.3	66.7	428.8
Saudi Arabia	4275.2	18.3	39.0	1172.5
Singapore	640.4	14.2	54.0	2095.1
South Korea	3689.4	9.2	36.1	1988.8
Sri Lanka	1232.8	8.7	35.8	198.3
Syria	1186.5	12.3	58.6	76.4
Thailand	4284.9	8.3	43.6	560.3
Vietnam	3779.6	5.7	53.4	322.8

Source: IDF 9th Edition 2019. Available from: https://www.diabetesatlas.org/en/

Socioeconomic Burden

Diabetes is associated with significant social challenges and economic impact at the individual, family, society, and national level [17]. Southeast Asian countries like India and Bangladesh had a higher diabetes risk among the higher socioeconomic groups with lower education levels [18]. A recent report from India suggests that the direct cost of diabetes was estimated to range from INR 1198 per annum to INR 45,792 [19]. Per the IDF 9th edition, the mean annual expenditure per person for diabetes in Asia is reported in Table 17.2. These data indicate that economic burden owing to diabetes is huge; therefore, low-cost sustainable strategies and effective public health policy are warranted to curtail the growing diabetes burden.

Special Types of Diabetes in Asia

Of all diabetes, monogenic diabetes is estimated to represent 1–6% in Asians [20]. It includes maturity-onset diabetes of the young (MODY), maternally inherited diabetes with deafness (MIDD), neonatal diabetes, and other genetic syndromes such as lipodystrophies, Bardet-Biedl syndrome, and Wolfram syndrome [21, 22]. In an East Asian study (2019), 109 participants with diabetes out of 2090 were suspected to have monogenic diabetes of whom 23 (21.1%) harbored the pathogenic genetic variants of monogenic diabetes. Around 14 had pathogenic/likely pathogenic variants of common maturity onset diabetes of the young (MODY) genes which were identified in GCK, HNF1A, HNF4A, and HNF1B [21].

Identifying monogenic diabetes cases is challenging because genetic testing can be expensive and awareness is low. Appropriate clinical approaches for proper diagnosis are vital including history collection—onset of disease, family history, physical examination, biomarkers—C-peptide, pancreatic autoantibodies, lipid profiles and high-sensitivity C-reactive protein (CRP), and genetic risk scores. Further, screening and diagnosis for monogenic forms of diabetes require high-quality testing methods, including multiple gene sequencing tests, and knowledge of database searches related to genomes, exomes, and alleles [23, 24]. However, population-based studies in monogenic diabetes are limited. Focus on population-wide prevalence studies across all age groups could aid in better understanding its epidemiology [23].

Fibrocalculous Pancreatic Diabetes (FCPD)

FCPD is another rare form of diabetes secondary to chronic calcific pancreatitis, with no alcohol abuse and mainly concentrated in the tropical regions among malnourished young individuals [25, 26]. For example, an Indian study conducted between 2014 and 2016 involving 891 patients with diabetes found 0.34% cases to have FCPD. All FCPD patients were aged between 35 and 45 years, from low socioeconomic strata, and consumed a high percentage of carbohydrates [27].

Disparities in Diabetes Care in Asia

It is well known that socioeconomic inequality exists in diabetes with higher incidence and mortality among lower socioeconomic groups. A recent study from Japan found that lower income and older age increased the risk of hospitalization and in-hospital mortality. Further, sex-specific health inequalities were observed. Males with lower socioeconomic status had greater hospital morbidity, mortality, and poorer oral hypoglycemic agent medication adherence as compared to females [28]. Irregular visits to the physician and lower socioeconomic status tended to have poor glycemic control among patients. Larger inequalities in health and healthcare utilization were seen among patients with diabetes in China. Demographic structure, consumption behavior, and occupational socioeconomic status were found to be major contributors to higher rates of underdiagnosis and under-medication [29]. The prevalence of diabetes and treatment was influenced by socioeconomic factors leading to inequalities among diabetic middle-aged and elderly adults in China [30].

The coverage of recommended pharmacological and non-pharmacological diabetes treatment in selected Asian countries is shown in Table 17.3. In a secondary analysis of cross-sectional surveys from 55 low- and middle-income countries (LMICs), researchers assessed coverage of three pharmacological and three non-pharmacological treatments among people with diabetes [31]. The self-reported diabetes treatment coverage was based on population-level monitoring indicators recommended in the 2020 WHO Package of Essential Noncommunicable Disease Interventions. Overall, *4.6% (3.9–5.4) of individuals with diabetes self-reported meeting need for all treatments recommended for them*. Coverage of glucose-lowering medication was 50.5% (48.6–52.5); antihypertensive medication was 41.3% (39.3–43.3); cholesterol-lowering medication was 6.3% (5.5–7.2); diet counseling was 32.2% (30.7–33.7); exercise counseling was 28.2% (26.6–29.8); and weight-loss counseling was 31.5% (29.3–33.7). Asian countries at higher-income levels tended to have greater coverage. Female sex and higher age, body mass index, educational attainment, and household wealth were also associated with greater coverage. In summary, this

Table 17.3 Coverage of essential diabetes treatment in selected Asian countries

Country	HAQ-index (diabetes)	Glucose lowering medication	Antihypertensive medication	Cholesterol lowering medication	Diet counseling	Exercise counseling	Weight-loss counseling
Bangladesh	56	64.3	59.5	NA	NA	NA	NA
Bhutan	57	40.2	43.7	1.7	37.5	33.8	40.4
Cambodia	52	59.8	57.3	5.4	46.8	45.8	53.6
China	85	57.1	50.7	NA	16.9	NA	11.9
India	65	29.2	30.4	NA	NA	NA	NA
Indonesia	34	19.6	19	4.8	19.5	14.2	14
Laos	52	55.9	42.3	1.2	46.4	46.4	53.7
Myanmar	48	56.8	48.8	1.9	39.3	30.5	27.8
Nepal	58	53.8	36.7	0	33.7	28.5	28.3
Timor-Leste	65	14.3	44	0	10	10	9.5
Vietnam	64	64.2	36.6	16	42.8	39.3	31.9

Source: Flood et al. Lancet Healthy Longevity, 2021 [31]. Coverage for each indicated is reported in percentage. *HAQ* = healthcare access and quality for diabetes sourced from the GBD 2018 Lancet paper [32]

analysis concluded that fewer than *one in ten people with diabetes in LMICs receive coverage of guideline-based comprehensive diabetes treatment*. Given that diabetes is considered a tracer condition for examining health systems, these findings indicate that many countries face challenges in achieving universal health coverage.

Furthermore, a 2019 study uncovered poor management of diabetes along the care cascade (i.e., diabetes diagnosis, treatment, and control rates), indicating large unmet need for diabetes care across 28 LMICs. This analysis showed that the performance across the diabetes care cascade varied by World Bank income group and individual-level characteristics, particularly age, educational attainment, and BMI. Figure 17.3 shows the various stages of the care cascade as diagnosed, lifestyle advice, and/or medication given ("treated") and controlled (HbA1c <8.0%). Total unmet need for diabetes care (defined as the sum of those not tested, tested but undiagnosed, diagnosed but untreated, and treated but with diabetes not controlled) was 77.0% (95%CI: 74.9–78.9%). Older age, education, and higher BMI were associated with higher odds of being tested, being treated, and achieving control [33].

Several reports from the Asian region suggest an inadequate access, quality, and coverage of health services related to diabetes prevention and treatment. Figure 17.4 summarizes the key barriers to diabetes care in Asia.

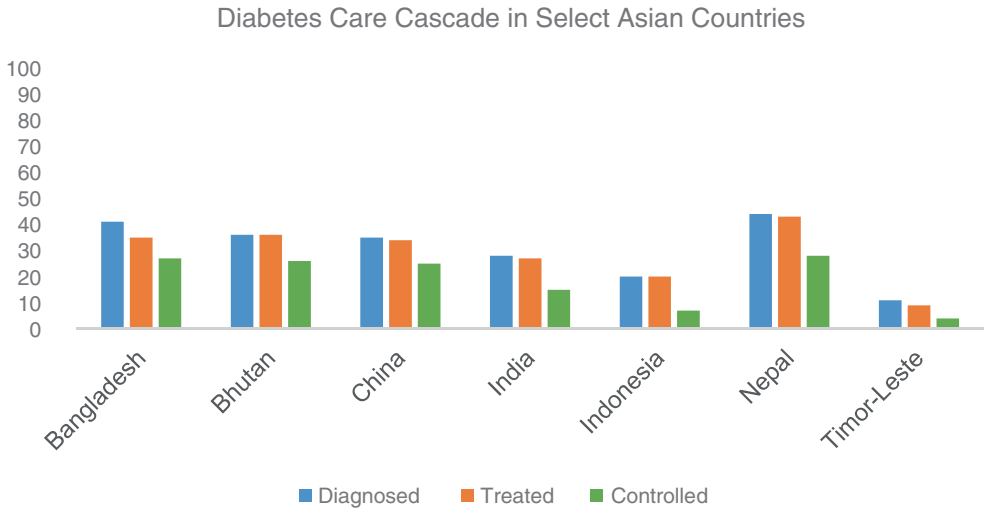

Fig. 17.3 Diabetes diagnosis, treatment, and control rates in selected Asian countries

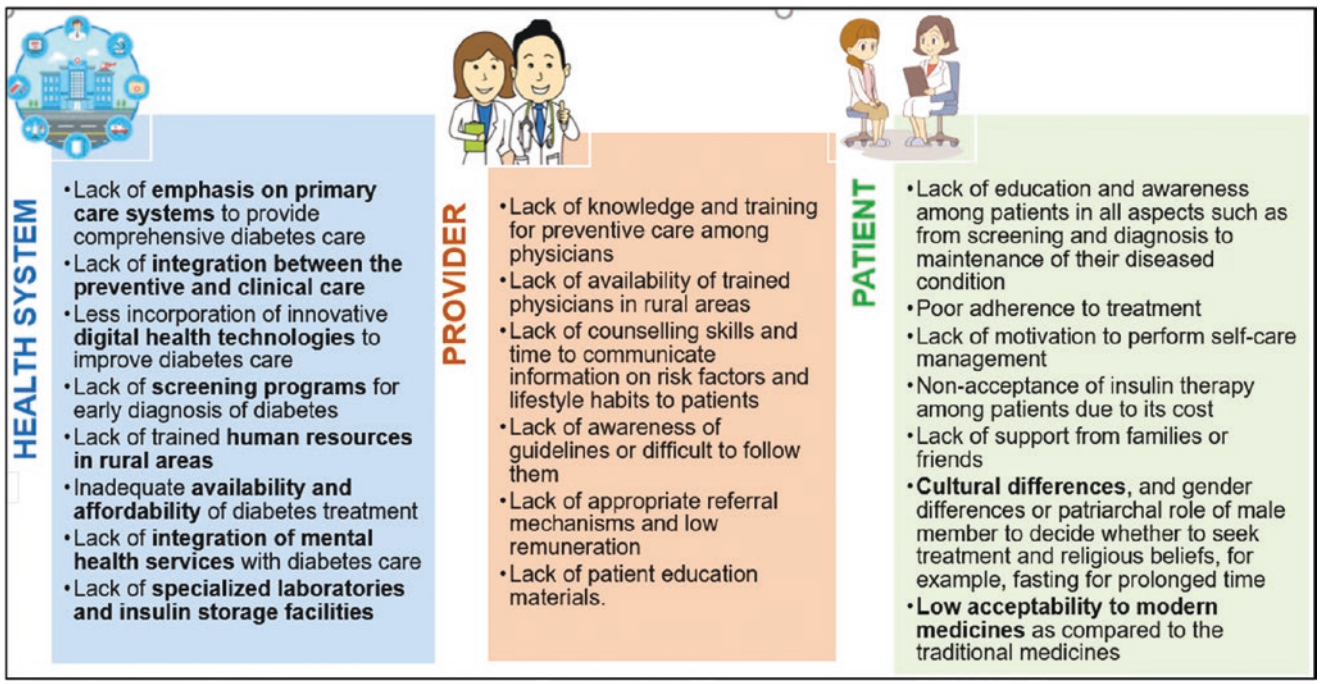

Fig. 17.4 Patient, provider, and health system level barriers to diabetes care in Asia

Management of Diabetes in Asia

Diabetes management involves both non-pharmacological and pharmacological approaches to prevention and treatment. Below we briefly describe the key recommendations for the prevention and management of diabetes in Asian context.

Non-pharmacological Approaches

Lifestyle Modification

Type 2 diabetes can be effectively controlled by simple lifestyle modification including the change in lifestyle habits (tobacco cessation, healthy diet, physical activity, and moderate alcohol consumption). Lifestyle advice should be given to all people with diabetes at the time of diagnosis. A systematic review and meta-analysis found that a low-carbohydrate diet and daily moderate- to high-intensity physical activity results in clinical improvements in people with type 2 diabetes [34].

Medical Nutrition Therapy (MNT)

MNT is beyond calorie restriction and dietary portion control. MNT is a lifestyle-transforming process in the management of diabetes. Asian countries such as India, China, Japan, Korea, and Thailand have huge cultural and culinary diversity which can be challenging. Therefore, designing individualized diet plan as a part of MNT should consider cultural, regional, and economical factors which will motivate individual to engage in healthy dietary habits. In the Asian context, guidelines recommend that carbohydrates should be limited to 50–60% of total calorie intake. Complex carbohydrates should be preferred over refined products. Fiber intake should be 25–40 g/day. The protein intake should be maintained at about 15% of total calorie intake. The quantity of protein intake depends on age, sarcopenia, and renal dysfunction. Nonvegetarian foods are sources of high-quality protein; however, intake of red meat should be avoided. Further, fats should be restricted to <30% of total calorie intake. Oils with high monounsaturated fatty acid (MUFA) and polyunsaturated fatty acid (PUFA) should be used. The use of two or more vegetable oils is recommended in rotation. Saturated fat (butter, coconut oil, margarine, ghee) intake should be less than 10% of total calories/day (<7% for individuals having high triglycerides). The use of partially hydrogenated vegetable oils (Vanaspati) as the cooking medium should be avoided. Reheating and refrying of cooking oils should be avoided. Diet rich in fruits, leafy vegetates, nuts, fiber, whole grains, and unsaturated fat is recommended. Food plate should include pulses, legumes, unprocessed vegetables, and low-fat dairy. Sugar-sweetened beverages are best avoided. Artificial sweeteners may be consumed in recommended amounts. Overall salt consumption should be <5 g/day (with sodium consumption <2300 mg/day). Smoking cessation should be advised to all. Smoking cessation therapies may be provided under observation for patients who wish to quit in a step-wise manner.

Further, a structured model of care (MOC) has been proposed for resource-constrained settings to improve pregnancy outcomes of Asian Indian women with gestational diabetes mellitus (GDM). Under the MOC, 212 women with GDM were followed through pregnancy, of whom 33 (15.6%) required insulin and 179 (84.4%) were managed with MNT and physical activity which reported that implementation of a structured MOC for women with GDM helped achieve improved pregnancy outcomes similar to those without GDM [35].

Physical Activity

Adoption of physical activity is very critical part of prevention and management of type 2 diabetes and its complications. A recent systematic review with meta-analysis assessed the effect of physical activity interventions in prediabetes and found that physical activity can help to slow down the progression of disease in individuals with prediabetes and thus reduces the morbidity and mortality associated with type 2 diabetes [36]. A minimum of 150 min/week of physical activity is recommended for healthy Asians due to the high predisposition to develop T2DM. The exercise regimens may consist of (a) ≥30 min of moderate-intensity aerobic activity each day, (b) 15–30 min of work-related activity, and (c) 15 min of muscle-strengthening exercises (at least 3 times/week). Further, recent Indian diabetes guidelines also recommend yoga practices including asanas (involving postures), pranayama (involving breath), and dhyana (involving meditation) as a part of holistic management of type 2 diabetes [37]. The use of monitoring tools like accelerometers, GPS units, pedometers, mobile-based apps, or devices to measure the intensity and duration of physical activity may be encouraged.

Pharmacological Approaches

The pharmacological management of diabetes is mainly divided into oral antidiabetic drugs (OADs), insulin therapy, and non-insulin injectable therapy.

Oral Antidiabetic Drugs (OADs)

Most commonly used OADs for the management of diabetes among Asians include biguanides (e.g., metformin), sulfonylureas (e.g., glimepiride), meglitinides (e.g., repaglinide), thiazolidinediones (e.g., pioglitazone), dipeptidyl peptidase IV inhibitors (e.g., sitagliptin), and α-glucosidase inhibitors (e.g., acarbose). As the first-line treatment for diabetes, metformin is recommended in combination with lifestyle interventions at the time of diagnosis. Further, initiation or dose increment of OADs requires monitoring the response through blood glucose monitoring every 2–3 months. Further, customization of OAD therapy depends up on the individualized target HbA1c for each patient based on age, duration of diabetes, comorbidities, cost of therapy, hypoglycemia risk, weight gain, and durability. Further, a recent meta-analysis of randomized trials assessed the impact of ethnicity on the glucose-lowering efficacy of the newer oral agents, sodium–glucose cotransporter 2 inhibitors (SGLT-2i), glucagon-like peptide 1 receptor agonists (GLP-1RA), and dipeptidyl peptidase 4 inhibitors (DPP-4i), which found that the glucose-lowering efficacy of SGLT-2i, and to a lesser extent DPP-4i, was greater in studies of predominantly Asian ethnicity compared with studies of predominantly White ethnicity. There was no difference seen by ethnicity for GLP-1RA [38].

Insulin Therapy

The choice of injectable insulin in type 2 diabetes mellitus is based on clinical, pharmacological, and psychosocial factors. In the Asian Indian context, factors like cost, quality of insulin, and cold chain maintenance must be considered. Patients who are failing to achieve glycemic targets on oral agents should be given insulin therapy. Evidence from clinical trials suggest that insulin glargine combined with oral antidiabetic drugs in the Asian and Chinese population with type 2 diabetes mellitus at a lower HbA1c can potentially lead to greater glycemic control [39].

Non-insulin Injectable Therapy (Glucagon-Like Peptide 1)

GLP-1 analogues are viable second-line or third-line option for the management of patients with uncontrolled hyperglycemia. Glucagon-like peptide 1 can be considered in overweight/obese patients as second-line therapy in patients with metformin inadequacy and as first-line therapy in patients with metformin intolerance. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) reduce HbA1c, fasting plasma glucose, and in particular postprandial glucose levels, and slow gastric emptying while minimizing the risk of hypoglycemia and weight gain and may be considered as a treatment option for East Asian patients with inadequately controlled diabetes by oral antidiabetic drugs (OADs) or basal insulin [40].

Management of Special Types of Diabetes (Monogenic Forms and FCPD)

Patients with monogenic diabetes are sensitive to low doses of sulfonylureas in the initial stages. A few patients may need insulin as the beta cell defect progresses [41]. However, most patients with FCPD require insulin injections. Early diagnosis and treatment of FCPD patients, in tropical as well as nontropical countries, along with adequate glycemic control with regular monitoring, pain relief, management of macro- and micronutrient requirements, and monitoring of pancreatic function are essential to improve quality of life in FCPD patients [26, 41].

Newer Approaches to Diabetes Management in Asian Context

In the first edition of the book chapter on Diabetes Management in Asia, we have previously described in detail about both diabetes prevention and care models including successful examples from Asia. Here we present an updated information on the evidence from randomized trials on the newer strategies that have been evaluated to prevent or manage diabetes in Asia.

The Japan Diabetes Optimal Integrated Treatment for three major risk factors of cardiovascular diseases (**J-DOIT3**) study, a multicenter, open-label, randomized controlled trial involving 81 clinical sites in Japan, randomly assigned 2542 patients with type 2 diabetes aged 45–69 years to receive conventional therapy for glucose, blood pressure, and lipid control or intensive therapy. Over a median follow-up duration of 8.5 years (IQR 7.3–9.0), the primary outcome defined as a composite of myocardial infarction, stroke, revascularization, and all-cause mortality occurred in 109 patients in the intensive therapy group and in 133 patients in the conventional therapy group (hazard ratio [HR] 0.81, 95% CI 0.63–1.04; $p = 0.094$). Although the trial showed inconclusive benefits of further intensified multifactorial intervention compared with usual care for the prevention of a composite of major adverse cardiovascular events, the trial results suggest a potential benefit of an intensified intervention for the prevention of cerebrovascular events in patients with type 2 diabetes [42].

Another randomized, open-label, multicenter trial (**INDEPENDENT**) conducted among type 2 diabetic patients at four urban diabetes clinics in India evaluated a collaborative care model designed to improve depression and diabetes and

its microvascular and macrovascular complications. Patients with diabetes and depression symptoms were randomized to intervention group and control group. Intervention group received collaborative care which included 12 months of self-management support from nonphysician care coordinators, decision support electronic health records (DS-EHR) facilitating physician's treatment adjustments, and specialist care reviews. This trial showed that with the 12 months of collaborative care, significant improvements were seen in depressive symptoms and cardio-metabolic measures at 24 months among intervention group vs. control group [43]. Further cost-effectiveness analysis results from the INDEPENDENT Trial and CARRS-Translation Trial in India are underway and will be available in the near future. Preliminary findings from the cost-effectiveness analysis suggest that these diabetes care models are likely to be cost-effective to manage poorly controlled type 2 diabetes and depression in resource constraint settings.

A 2020 trial-based economic evaluation of **D-CLIP trial** conducted in India found that a stepwise approach for identification of high-risk individual and diabetes prevention would cost Parity Adjusted International Dollars (Int$) 145 to screen for and reduce diabetes incidence by 1% point, and Int$ 14,539 per diabetes case prevented and/or delayed, and Int$ 14,986 per quality-adjusted life-year gained, suggesting that a stepwise diabetes screening and prevention strategy is likely cost-effective, even in a low-income to middle-income country setting [44]. The findings of this economic evaluation can support more effective allocation of scarce healthcare resources for screening and stepwise approach to manage screen-detected diabetes in South Asia.

Impact of COVID-19 Pandemic on Diabetes Care and Potential Role of Digital Health Technologies

Since the World Health Organization's declaration of the COVID-19 pandemic in March 2020 [45], COVID-19 has remained rampant globally. In global case studies, older age, men, and the presence of comorbidities such as diabetes, cardiovascular diseases, chronic kidney disease, as well as regional differences in healthcare access and resources were identified as risk factors for mortality due to COVID-19-related factors [46]. Further, the mobility restrictions and lockdowns implemented to control COVID-19 have placed unintended direct and indirect stress on healthcare access by limiting access to healthy foods, exacerbating food insecurity among vulnerable populations, and limiting regular physical activity. A study from India found an association between state-level COVID-19 cases and deaths with diabetes, among other chronic conditions [47]. Another study found that the largest reductions in primary care contacts have been observed for contacts for diabetes-related emergencies (OR 0.35 [95% CI 0.25–0.50]) [48, 49].

Therefore, we need to reimagine the current healthcare system to provide alternative approaches to deliver care beyond COVID-19 and more investment in preventive care, building resilient primary healthcare systems as well as expanding financial protection through universal health coverage, to improve outcomes for patients with chronic conditions and prevent more people from developing these diseases amidst the current COVID-19 crisis [49]. Digital health technologies have transformed the way of delivering health services, particularly for chronic conditions to improve health outcomes. Mobile health (m-health) is the most promising and expanding approach in high-income countries to support the achievements of health goals and self-care management. mHealth strategies include short messaging services (SMS), remote monitoring devices, and other mobile-based applications. m-Health is a user-friendly health technology that enables and empowers people in capturing and monitoring health data. m-Health can foster patient engagement in diabetes self-care and potentially improve the interactions between patient and healthcare providers, particularly in resource constraints settings of Asia region.

For example, in India, a cluster randomized trial in 40 community health centers involving 3698 patients evaluated an android application used on a tablet computer that was capable to store health records electronically, enabling long-term monitoring and follow-up, and generated tailored management plan for hypertension, diabetes and comorbid depression, alcohol, and tobacco use. Further, SMS reminders were sent to the intervention group patients for follow-up and medication adherence. At 1-year follow-up, there was a greater reduction in the systolic blood pressure in the intervention group, but it did not reach statistical significance [50]. More recently, the researchers have successfully translated the mHealth intervention from research to service delivery mode in India, and it has been adopted by the state government of Tripura in India to manage hypertension and diabetes at the community health center level. Future work on mHealth to improve diabetes care should utilize consumer facing design thinking principles involving key stakeholders (patients, caregivers, physicians, and health administrators) to improve the acceptability, adoption, and effectiveness of mHealth strategies in patients with diabetes.

Conclusions

After three decades of intensive research, the benefits of blood glucose, blood pressure, and blood cholesterol lowering in patients with diabetes cannot be undervalued. Although proven and safe drugs now exist to meet treatment goals for people with diabetes, there remain enormous care gaps, especially in young patients and socially disadvantaged population. In view of the complexity of diabetes and patients'

pluralistic needs in Asia region, doctors and patients need to be fully informed and given time and support to build trusting relationships, supported by periodic assessments with access to free medications and self-monitoring tools, to minimize clinical inertia and nonadherence to prescribed therapy. The recent trials aimed to improve cardiovascular outcomes in patients with diabetes reminds us once again of the urgency of using advocacy, polices, and systems to ensure that patients with diabetes are managed by trained multidisciplinary healthcare teams, with regular feedback and monitoring of treatment targets to make optimal diabetes care a reality.

Further, constructing a regional infrastructure with guidelines, policies, and regional and centralized electronic health records to promote routine clinic-level diabetes patients' data collection, storage, and management along with diabetes-specific registries by professional societies and organizations will be effective to advance diabetes care. Research toward population-based management of both classical and special forms of diabetes will pave path toward a systematic approach to screening, diagnosis, and precision treatment of diabetes overall.

Points to Remember

- Asia region has one of the highest age-standardized disability-adjusted life years (DALYs) associated with diabetes mellitus.
- Southeast Asian countries like India and Bangladesh had a higher diabetes risk among the higher socioeconomic groups with lower education levels.
- Diabetes management involves both non-pharmacological and pharmacological approaches to prevention and treatment.
- Pharmacological management of diabetes is divided into oral antidiabetic drugs (OADs), insulin therapy, and non-insulin injectable therapy.
- Non-pharmacological management of diabetes is divided into lifestyle modification, medical nutrition therapy (MNT), and physical activity.

Multiple Choice Questions

1. Which region of world has the highest age-standardized disability-adjusted life years (DALYs) associated with diabetes mellitus?
   (a) Central Europe
   (b) Mediterranean and Middle East
   (c) **Asia**
   (d) Western Europe
2. Which Asian country has the largest number of adults with diabetes?
   (a) North Korea
   (b) **China**
   (c) Japan
   (d) Sri Lanka
3. Prevalence of diabetic neuropathy appears to be higher among which Asian country.
   (a) Pakistan
   (b) **Sri Lanka**
   (c) Iran
   (d) Malaysia
4. Which is the rare for, of diabetes among the malnourished young individuals with no alcohol abuse?
   (a) **Fibrocalculous pancreatic diabetes**
   (b) Maternally inherited diabetes with deafness
   (c) Neonatal diabetes
   (d) Maturity-onset diabetes of the young
5. What are the non-pharmacological approaches for diabetic management in Asia?
   (a) Lifestyle modification only
   (b) Lifestyle modification and insulin therapy
   (c) Medical nutrition therapy (MNT) only
   (d) **Lifestyle modification, medical nutrition therapy and physical activity**
6. Most commonly used oral antidiabetic drugs in Asia:
   (a) Biguanides
   (b) Thiazolidinediones
   (c) Biguanides and sulfonylureas
   (d) **All of the above**
7. As a part of medical nutrition therapy (MNT), what are the recommendations for the Asian population?
   (a) Carbohydrates should be limited to 50–60% of total calorie intake along with <5 g/day of salt consumption.
   (b) Fiber intake should be more than 40 g/day.
   (c) Diet rich in fruits, leafy vegetates, nuts, fiber, whole grains, and unsaturated fat.
   (d) Oils with high unsaturated fatty acid should be used.
   (e) **Both a and c**.
   (f) Only c option.
8. Exercise regimens among Asian diabetic population:
   (a) <30 min of moderate-intensity aerobic activity each day
   (b) >15 min of moderate-intensity aerobic activity each day
   (c) **≥30 min of moderate-intensity aerobic activity each day**
   (d) 20 min of moderate-intensity aerobic activity each day

9. Identify the barriers to diabetic care in Asia at healthcare system level.
   (a) Lack of integration between preventive and clinical care
   (b) Lack of patient education materials
   (c) Lack of emphasis on primary care systems to provide comprehensive diabetes care
   (d) **Both a and b**
10. What are the intervention components of the INDEPENDENT trial for type 2 diabetes patients?
   (a) Self-management support from nonphysician care coordinators
   (b) Decision support electronic health records
   (c) **Both a and b**

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Further Reading

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Diabetes Management in Latin America

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Epidemiology of Type 1 Diabetes Mellitus in Latin America and the Caribbean

The International Diabetes Federation estimates that in 2019, there were a total of 14,750 incident cases of type 1 diabetes in the age group 0–19 years (11,970 in the age group 0–14 years) and 153,700 prevalent cases in the same age group (83,240 in the age group 0–14 years) in Latin America [1]. The International Diabetes Federation data does not provide any data on the incidence or prevalence in older age groups. Many authors have stated that there is a paucity of data on the epidemiology of type 1 diabetes in Latin America [2, 3].

Temporal Trends

Globally, a 3–4% increase in incidence has been found for type 1 diabetes [4]. In Latin America, different studies have shown different trends. An increase (4%) in incidence was seen in Brazil over the period 1986–2006 [5]. In Mexico, a decrease in incidence was found between 2000 and 2018 (3.4–2.8 per 100,000) [6]; in contrast, another study by Gomez-Diaz et al. [7] also in Mexico showed an increase (3.4–6.2 per 100,000) between 2000 and 2010. Studies in Chile from 2000 to 2004 [8] and 2006 to 2014 [9], respectively, found increase of 5.4–8.3 per 100,000 population and 10.2–13.8 per 100,000 population, respectively. The studies by Negrato et al. [5] in Brazil, Garfias et al. in Chile [9] and Wacher et al. [6] in Mexico show wide variations in incidence rates over the periods studied.

Determinants and Drivers of Incidence of Type 1 Diabetes in Latin America

As in other world regions, the determinants and drivers of the incidence of type 1 diabetes are varied and as of yet unknown [4]. Various studies in Latin America have investigated different factors leading to changes in the condition's epidemiology. It has been noted that in Latin America, there is a link between the incidence of type 1 diabetes and European origin versus people of indigenous or African origin [2, 9–12].

Geographical differences in incidence have been noted in Brazil. In the Northeast, an incidence rate of 1.8 per 100,000 person-years was found in contrast to 10.4 per 100,000 person-years in the Southeast and 12.7 per 100,000 and 12 per 100,000 persons-year in 2 Southern Regions [3]. Peaks in incidence in Mexico were found to correspond to years of influenza outbreaks [6]. In an ecological model in Chile influenza, respiratory infections and environmental particulate matter were found to lead an increase with developing type 1 diabetes [13].

Differences in incidence based on gender were found in Mexico [6]. No seasonality of incidence is found in Cuba [14]. Shorter duration of breastfeeding equalled an increased risk of type 1 diabetes in a study in Brazil [15]. Enterovirus infection was found to be a risk factor for type 1 diabetes in different studies in Cuba [16]. Collado-Mesa et al. [10] found

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a strong correlation between per capita supply of milk and incidence and prevalence of type 1 diabetes, as in other non-Latin American settings, as well as a correlation of wealth-related indicators for prevalence, but not for incidence. With regard to wealth as a determinant of type 1 diabetes, in Brazil and Chile, an increase in incidence was found in higher socio-economic groups [17, 18].

Genetic traits known to be a risk for increased incidence of type 1 diabetes were identified in Mexico [19] and Uruguay [20] (HLA-DQ allele), Colombia (RNASEH1) [21], Argentina and Colombia (rs763361 in CD226 and rs6822844 at the IL2-IL21 region) [22, 23], Chile (gene polymorphisms of PD-ligands (PD-L1 and PD-L2)) [24] and Brazil (rs763361 variant of CD226 gene (TT genotype) and HLA DQ2.5 and DQ8 haplotypes) [25–28]. In studying the HLA region which is a known genetic risk factor for type 1 diabetes globally, Conte Santo et al. [29] suggested that these alleles come mainly from the European population in Brazil through colonization and migration.

Age at Diagnosis

Most studies in Latin America show variations in the incidence rates for different ages [5, 7, 9, 17, 30]. A study in Brazil found that the incidence rate in infants and toddlers decreased during the period 1980–2014 but increased in children above the age of 10 [30]. Different mean ages at diagnosis were found in different Brazilian studies: 6.8 [30], 8.9 [5] and 11.3 [17] years. In Chile, the incidence was found to have increased especially in children under the age of 4 [8].

Delivery and Quality of Care

In many Latin American countries, type 1 diabetes care is predominantly provided in a hospital setting [3, 31, 32]. Diabetes control as measured by HbA1c in many Latin American countries is relatively poor, with, for example, in Mexico 18% of subjects having an HbA1c less than 7% and 35% more than 9% [33]. The problems with quality of diabetes care in Latin America have been identified for quite some time, with the QUALIDIAB network in 2001 already presenting data on the low quality of diabetes management in the region [34]. More recent studies in Brazil show that children, adolescents and adults with type 1 diabetes do not receive the necessary tests and screening for complications in comparison to international guidelines and ideal management of type 1 diabetes [35–37]. It could be argued that the poor delivery and quality of care is responsible for low levels of adherence found in Latin America [38].

Access to Care and Insulin

Cost of diabetes care can be a burden for the family. In some Latin American countries, some elements of diabetes care are provided for free, for example, insulin and consultations in Nicaragua [31]. In Mexico, it was found that average family costs of treatment and monitoring for type 1 diabetes were US$ 1690 which represents a substantial cost [39]. The highest cost was for self-monitoring representing 53% of total cost and insulin 15% of total cost. From a nationwide study in Brazil, similar results were found with insulin administration supplies and self-monitoring representing 53% of total costs of US$ 1319 per year [40]. Regional differences in the average annual per capita spending for type 1 diabetes care were found in Brazil with a range from US$ 1148 to US$ 1466 [32]. Although many aspects of diabetes care are provided for free in the public sector in Latin American countries, these are often not available [41]. With different populations accessing different services dependent on their family or their income or employment status, different outcomes for type 1 diabetes are seen with, for example, in Brazil, people with private insurance having better diabetes management than those in the public health system [42]. These socio-economic and educational differences were also linked to better access to insulin analogues and insulin pumps, with Caucasians, those with higher economic status and more years of schooling having better access in Brazil [43]. In other Brazilian studies, socio-economic [32, 44–46] and education [47] levels impacted diabetes care. Similar results were also found in Argentina with socio-economic and familial factors associated with poor control [48].

This challenge of overall access in the context of Universal Health Coverage and inequality is addressed in a study in Chile, highlighting that although coverage exists in Chile, people still face challenges accessing the care they should receive [49].

Complications

Due to challenges in the delivery of care and barriers to access, poor management and high rates of complications have been found in Latin America. In a nationwide survey of glycaemic control in people with diabetes, 87% of people with type 1 diabetes had an HbA1c above 7% [50]. Regarding complications, in a nationwide, cross-sectional study in Brazil of people with type 1 diabetes, 35% presented diabetic retinopathy and 12% presented vision-threatening diabetic retinopathy [51]. A cohort study in Brazil found that 70% of deaths were due to end-stage renal disease, macrovascular disease or acute complications of diabetes, mainly diabetic ketoacidosis, with a threefold increase in mortality [52]. Another study in Southern Brazil found that the leading

factor in people presenting diabetic ketoacidosis was non-compliance to their treatment [53].

Epidemiology of Type 2 Diabetes Mellitus in Latin America and the Caribbean

The region of Latin America and the Caribbean is highly heterogeneous. Although sharing geographic, language and some ethnic similarities, it presents a significant diversity regarding genetic ancestry and environmental exposures. In addition, this region presents major inequalities [54, 55] which often manifest themselves as health disparities [56], including differences in the obesity burden [57] and life expectancy [58] which influence the development of type 2 diabetes.

The NCD Risk Factor Collaboration (NCD-RisC) proposed the following sub-regions, which are helpful in terms of comparison [59]: Andean Latin America, Caribbean, Central Latin America and Southern Latin America. A similar sub-region classification is available when analysing the Global Burden of Disease (GBD) data [60].

Diabetes data, especially country-specific, are scarce for most of the region, but increased effort has been made to aggregate and synthesize the available data by global collaborations such as the International Diabetes Federation, which produces biannually the International Diabetes Federation Diabetes Atlas [61], the GBD Study, with its multiple publications on disease and risk factor frequency and burden [60], and the NCD-RisC, with its multiple and insightful studies, predominantly of prevalence [62]; finally, there has been a constant increase of systematic reviews and meta-analyses.

Prevalence

According to the International Diabetes Federation, in 2019, among those between 20 and 79 years old, 463 million people were living with diabetes worldwide, which is expected to increase to 700 million by 2045 based on population ageing and urbanization. Of these, 90% are estimated to have type 2 diabetes, and a total of 31.7 million were living in the South America and Central America region (including only the Spanish-speaking Caribbean nations), representing an 8% (95% CI: 6–11%) age-adjusted comparative diabetes prevalence, and ranking fifth among the seven world regions considered [61]. This estimate is expected to increase to 9% (95% CI: 7–13%) by 2045. The International Diabetes Federation aggregates Mexico with the non-Spanish-speaking Caribbean and North America to create the North America and Caribbean region. Discounting the United States and Canada, the remaining countries of this region were home to 13.8 million living with diabetes in 2019 [61]. It is worth noting that many individuals with diabetes do not know their diagnosis, which includes an estimated 36% of all individuals living with diabetes in Latin America and the Caribbean in 2019. Despite scarce country-level data being available for the region, the highest proportion of undiagnosed diabetes was found for Haiti (52%) and the lowest for Chile (21%) [61].

The Global Burden of Disease (GBD) estimated a type 2 diabetes prevalence of 6% (95% CI: 6–7%) for all low- and middle-income countries of the Latin America and Caribbean region in 2019 [60]. Over the last 10 years, Mexico and the two GBD sub-regions of Central Latin America and the Caribbean have consistently shown a considerably higher age-standardized prevalence than the global estimate (Fig. 18.1).

Brazil and Mexico had the highest absolute number of people living with diabetes in 2019 in Latin America: 16.8 and 12.8 million, respectively [61]. As for the International Diabetes Federation age-adjusted comparative prevalence, Belize was the country with the highest (17%; 95% CI: 14–19%) and Ecuador the one with the lowest (5%; 95% CI: 3–8%). Considering the countries with the largest populations, Brazil ranked 19th in age-adjusted prevalence (10%; 95% CI: 9–11%) and Mexico 4th (13%; 95% CI: 8–16%) [61] (Table 18.1). Brazil experienced an increase in diabetes crude prevalence of 91% over recent decades (from 1990 to 2019), according to the GBD data. The increase was primarily due to population ageing, as the age-adjusted increase was only 15% [60, 63]. Mexico's crude and age-adjusted prevalence increased somewhat more—by 114% and 22% [60]. Mexico's greater prevalence is believed to be principally due to its greater prevalence of risk factors, especially obesity. The Mexican 2018–2019 National Survey on Health and Nutrition (ENSANUT) estimated that 39% (95% CI: 37–40%) of adults were overweight and an additional 36% (95% CI: 34–37%) were obese, with the obesity prevalence having increased 42% from the year 2000. The latest increase (9% between 2012 and 2018) was higher than the previous one (6% between 2006 and 2012), indicating that the obesity and, consequently, the diabetes prevalence will likely continue to increase [64].

Except for Mexico (ranked 4th), the remaining top 10 countries, in terms of International Diabetes Federation age-adjusted comparative prevalence (Table 18.1) were all from the Caribbean region: Belize, British Virgin Islands, Puerto Rico, Barbados, Saint Kitts and Nevis, Antigua and Barbuda, Suriname, US Virgin Islands and Saint Vincent and the Grenadines [61]. Despite the scarcity of quality country-level data for the Caribbean region, resulting in higher estimate uncertainty, NCD-RisC reported that the largest increases in obesity and diabetes in the Americas between 1980 and 2014 were for the non-English-speaking (obesity

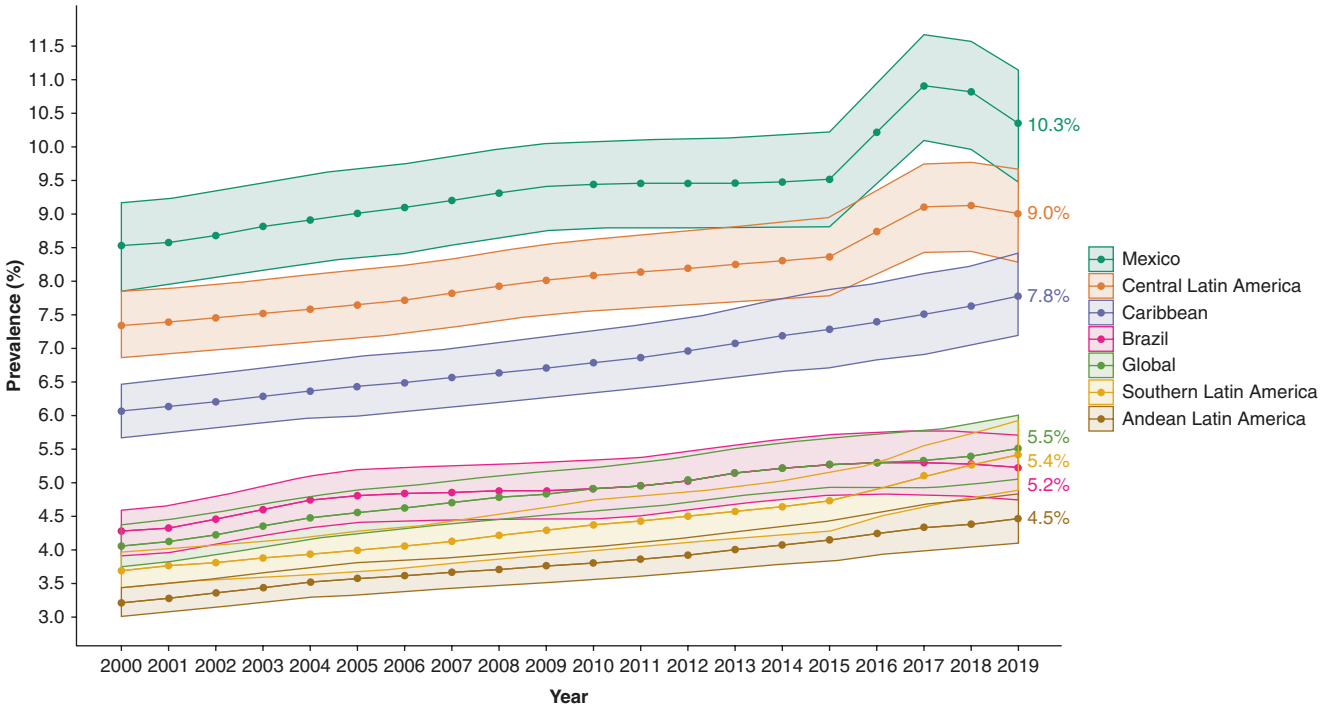

Fig. 18.1 Age-standardized prevalence (%) of type 2 diabetes on Latin American and Caribbean sub-regions for 2000–2019, data from the Global Burden of Disease

increase by 377% in men and 150% in women) and the English-speaking (diabetes increase by 23% in men and 22% in women) Caribbean sub-regions, respectively [62].

Three countries (Bolivia, Ecuador and Peru), usually classified together as the Andean Latin America sub-region, presented the first (5%; 95% CI: 3–8%), fourth (6%; 95% CI: 4–10%) and sixth (6%; 95% CI: 5–10%) lowest age-adjusted comparative prevalence, respectively [61] (Table 18.1). However, even though they presented the lowest rates, diabetes prevalence and management in these countries still represent major public health issues. A recent analysis estimated that the proportion of diabetes in these three countries attributable to each 5-unit BMI increase rose from 29% in 1980 to 50% in 2014 [65].

Incidence

Although of high importance to measure risk and changing risk over time for diabetes, the estimation of diabetes incidence usually requires much larger studies with a long-term follow-up and higher costs involved. Thus, there are scant diabetes incidence data available for Latin America and the Caribbean.

Age-period-cohort models are applied to the Mexico National Health and Nutrition Survey projected age-specific incidence estimates for 2010. For both men and women, the highest rate was in the 50–59 age interval (27.0/1000 in women and 23.3/1000 in men) [66]. The cohort study PERUDIAB estimated the diabetes incidence in urban areas of Peru as 19.5 per 1000; in contrast, the PERU MIGRANT study, in which more than half of the participants are from rural areas, estimated an incidence 50% lower [67]. The ELSA-Brazil (Longitudinal Study of Adult Health) cohort reported a diabetes incidence estimate of 2.0 per 100 person-years for Brazilian adults from six large capital cities [68].

Interventions focusing on improving known lifestyle and socioeconomic diabetes risk factors have demonstrated efficacy in decreasing the incidence of diabetes [69–71]; therefore, studies that address trends, current burden and management of these factors can be of great help in understanding the future risk of type 2 diabetes.

Mortality

Type 2 diabetes is well known to lead to increased mortality [72], disability and a lower quality of life [73] and, at the same time, to impose a heavy economic burden on the healthcare system [74], especially on low- and middle-income countries, such as most of those in Latin America and the Caribbean [75]. However, data on diabetes-related mortality in the region are scant. A recent meta-analysis reported that in Latin America, all-cause mortality in patients with self-reported diabetes was 149% (RR = 2.49; 95%CI: 1.96–3.15) higher than that of people without diabetes. For

Table 18.1 Number of individuals with diabetes, age-adjusted comparative prevalence of diabetes, and number of individuals with undiagnosed diabetes for Latin American and the Caribbean, data from the Diabetes International Diabetes Federation, 2019

Country or territory	GBD sub-region	Number of adults 20–79 years with diabetes in 1000s (95% confidence interval)	Diabetes age-adjusted comparative prevalence (%) in adults 20–79 years (95% confidence interval)	Diabetes age-adjusted comparative prevalence rank	Number of adults 20–79 years with undiagnosed diabetes in 1000s (95% confidence interval)
Bolivia	Andean Latin America	411.4 (337.5–636.3)	6.8 (5.6–10.4)	36	114.3 (93.8–176.8)
Ecuador	Andean Latin America	579.1 (351.3–904.9)	5.5 (3.4–8.9)	41	227.0 (137.7–354.7)
Peru	Andean Latin America	1385.0 (966.9–2244.2)	6.6 (4.6–10.7)	38	542.9 (379.0–879.7)
Antigua and Barbuda	Caribbean	9.3 (8.6–10.5)	13.1 (12.0–15.0)	7	2.8 (2.6–3.2)
Bahamas	Caribbean	26.9 (21.8–41.7)	8.8 (7.1–13.7)	26	8.1 (6.6–12.6)
Barbados	Caribbean	36.4 (32.4–42.1)	13.4 (11.9–16.0)	5	9.5 (8.5–11.0)
Belize	Caribbean	34.1 (29.6–39.3)	17.1 (14.9–19.7)	1	14.0 (12.2–16.2)
Bermuda	Caribbean	6.9 (5.9–8.0)	6.7 (5.6–8.0)	37	2.1 (1.8–2.4)
Cuba	Caribbean	1134.0 (1035.3–1236.5)	9.6 (8.8–10.6)	23	444.5 (405.9–484.7)
Dominica	Caribbean	6.3 (5.2–7.8)	11.6 (9.7–14.9)	13	2.3 (1.9–2.9)
Dominican Republic	Caribbean	578.8 (421.6–747.5)	8.6 (6.3–11.1)	28	226.9 (165.3–293.0)
Grenada	Caribbean	6.8 (5.2–9.0)	10.7 (8.4–14.2)	19	2.5 (1.9–3.3)
Guyana	Caribbean	50.4 (43.1–67.9)	11.6 (9.7–14.9)	12	18.5 (15.9–25.0)
Haiti	Caribbean	365.6 (246.9–602.4)	6.6 (4.5–10.6)	39	192.6 (130.0–317.3)
Jamaica	Caribbean	226.5 (181.8–284.8)	11.3 (9.1–14.3)	17	55.4 (44.5–69.6)
Puerto Rico	Caribbean	438.7 (368.9–521.3)	13.7 (11.5–16.4)	3	142.6 (119.9–169.4)
Saint Kitts and Nevis	Caribbean	5.3 (3.8–7.2)	13.2 (9.4–18.4)	6	1.6 (1.1–2.2)
Saint Lucia	Caribbean	14.8 (12.7–19.6)	11.6 (9.7–14.9)	11	5.5 (4.7–7.2)
Saint Vincent and the Grenadines	Caribbean	8.8 (7.4–11.2)	11.6 (9.7–14.9)	10	3.2 (2.7–4.1)
Suriname	Caribbean	47.9 (32.9–92.2)	12.5 (8.5–24.3)	8	17.6 (12.1–34.0)
Trinidad and Tobago	Caribbean	121.3 (100.2–161.6)	11.0 (9.0–14.9)	18	36.5 (30.2–48.6)
US Virgin Islands	Caribbean	12.4 (10.4–14.4)	12.2 (10.2–14.4)	9	3.4 (2.9–4.0)
Aruba	Caribbean[a]	11.6 (9.7–14.3)	11.6 (9.6–14.9)	15	3.5 (2.9–4.3)
British Virgin Islands	Caribbean[a]	3.1 (2.3–4.0)	14.2 (10.3–18.4)	2	0.9 (0.7–1.2)
Cayman Islands	Caribbean[a]	5.9 (5.3–6.8)	6.8 (6.2–8.0)	33	1.8 (1.6–2.1)
Curaçao	Caribbean[a]	19.7 (15.5–23.3)	11.6 (9.6–14.9)	14	5.9 (4.7–7.0)
Saint Maarten	Caribbean[a]	3.8 (3.4–4.4)	6.8 (6.2–8.0)	34	1.2 (1.0–1.3)
Colombia	Central Latin America	2836.5 (2017.4–3815.2)	7.4 (5.1–10.6)	30	1111.9 (790.8–1495.6)
Costa Rica	Central Latin America	353.0 (314.0–403.7)	9.1 (8.1–10.5)	24	138.4 (123.1–158.3)
El Salvador	Central Latin America	346.2 (302.8–448.3)	8.8 (7.7–11.3)	25	135.7 (118.7–175.7)
Guatemala	Central Latin America	782.2 (517.2–1174.9)	10.0 (6.8–14.9)	21	306.6 (202.7–460.6)
Honduras	Central Latin America	339.2 (235.9–558.3)	7.3 (5.0–12.0)	32	133.0 (92.5–218.8)
Mexico	Central Latin America	12,805.2 (7208.6–15,375.6)	13.5 (8.1–16.7)	4	4949.0 (2786.1–5942.7)
Nicaragua	Central Latin America	395.8 (259.1–542.1)	11.4 (7.4–15.6)	16	155.2 (101.6–212.5)

(continued)

Table 18.1 (continued)

Country or territory	GBD sub-region	Number of adults 20–79 years with diabetes in 1000s (95% confidence interval)	Diabetes age-adjusted comparative prevalence (%) in adults 20–79 years (95% confidence interval)	Diabetes age-adjusted comparative prevalence rank	Number of adults 20–79 years with undiagnosed diabetes in 1000s (95% confidence interval)
Panama	Central Latin America	206.1 (171.0–295.1)	7.7 (6.4–10.7)	29	67.0 (55.6–95.9)
Venezuela	Central Latin America	1403.6 (1052.2–2017.7)	7.0 (5.0–10.8)	35	727.1 (545.0–1045.2)
Argentina	Southern Latin America	1837.4 (1309.6–2712.4)	5.9 (4.4–8.5)	40	597.2 (425.6–881.5)
Chile	Southern Latin America	1262.2 (1081.3–1550.0)	8.6 (7.4–10.7)	27	271.5 (232.6–333.4)
Uruguay	Southern Latin America	196.0 (148.3–247.1)	7.3 (5.7–9.4)	31	63.7 (48.2–80.3)
Brazil	Tropical Latin America	16,780.8 (15,045.1–18,697.9)	10.4 (9.2–11.5)	20	7719.2 (6920.7–8601.0)
Paraguay	Tropical Latin America	372.7 (340.4–411.3)	9.6 (8.8–10.6)	22	146.1 (133.4–161.2)

[a] Not included on the Global Burden of Disease (GBD) sub-region classification

cardiovascular mortality, the increased risk observed was a 176% (RR = 2.76; 95% CI: 1.99–3.82) [76].

According to the GBD, Mexico was the country with the highest type 2 diabetes mortality rate in those less than age 70 in 2019 (28.9 per 100,000; 95% CI: 24.5–33.4), followed by Central America (20.4 per 100,000; 95% CI: 17.7–23.2) and the Caribbean (18.2 per 100,000; 95% CI: 14.7–22.3) sub-regions (Fig. 18.2). The lowest estimate was observed for Southern Latin America (7.9 per 100,000; 95% CI: 7.3–8.5) [60].

Local Quantification of Risk Factors

The aetiologies of type 2 diabetes are complex, involving nutritional, genetic and environmental factors. Over the last two decades, there were many surveys in Latin America and the Caribbean to assess diabetes prevalence and status of management, treatment and care goals. There is, however, still the need for more data to extend the understanding of diabetes prevention and high-quality care achievements across countries [77].

Globalization and urbanization have led Latin America and the Caribbean to experience a major dietary shift to less-healthful low-nutrient/high-density foods and sugary beverages, which contributed to the remarkable rise in obesity [78]. Globalization and urbanization also led to a more sedentary lifestyle [79], which may have contributed to the increasing burden of obesity and diabetes.

Glycaemic and weight control of those with diabetes are the main factors usually associated with better morbidity and mortality outcomes. Obesity has consistently increased in all sub-regions in the last decades [60]. A review of the glycaemic control in Latin America and the Caribbean reported that it varies across the region. However, no study reported a percentage above 54% for the attainment of HbA1c lower than 7%. The percentage of those achieving optimal glycaemic, blood pressure and LDL-cholesterol altogether was not higher than 9%. This review also observed that the glycaemic control attainment over the region was associated with higher socioeconomic status, having health insurance, and better access to healthcare services [77].

The genetic ancestry of those living in Latin America and the Caribbean is diverse and highly admixed. For example, African ancestry has been described as having a higher frequency in Puerto Rico or Dominican Republic, while in Mexico or Bolivia, it was Native American ancestry, and in Chile and Argentina, European [80]. While there have been studies indicating an association of African and Native American ancestry with type 2 diabetes, a high portion of this association may be due to socioeconomic inequalities [81].

Socioeconomic disparities in the region are known to be a subjacent cause of diabetes. They can cause diabetes through food insecurity, which is a barrier to healthy eating habits, and by leading to unsafe neighbourhood environments which impose obstacles to augmenting physical activity, as well as through more difficult access to health care and medication

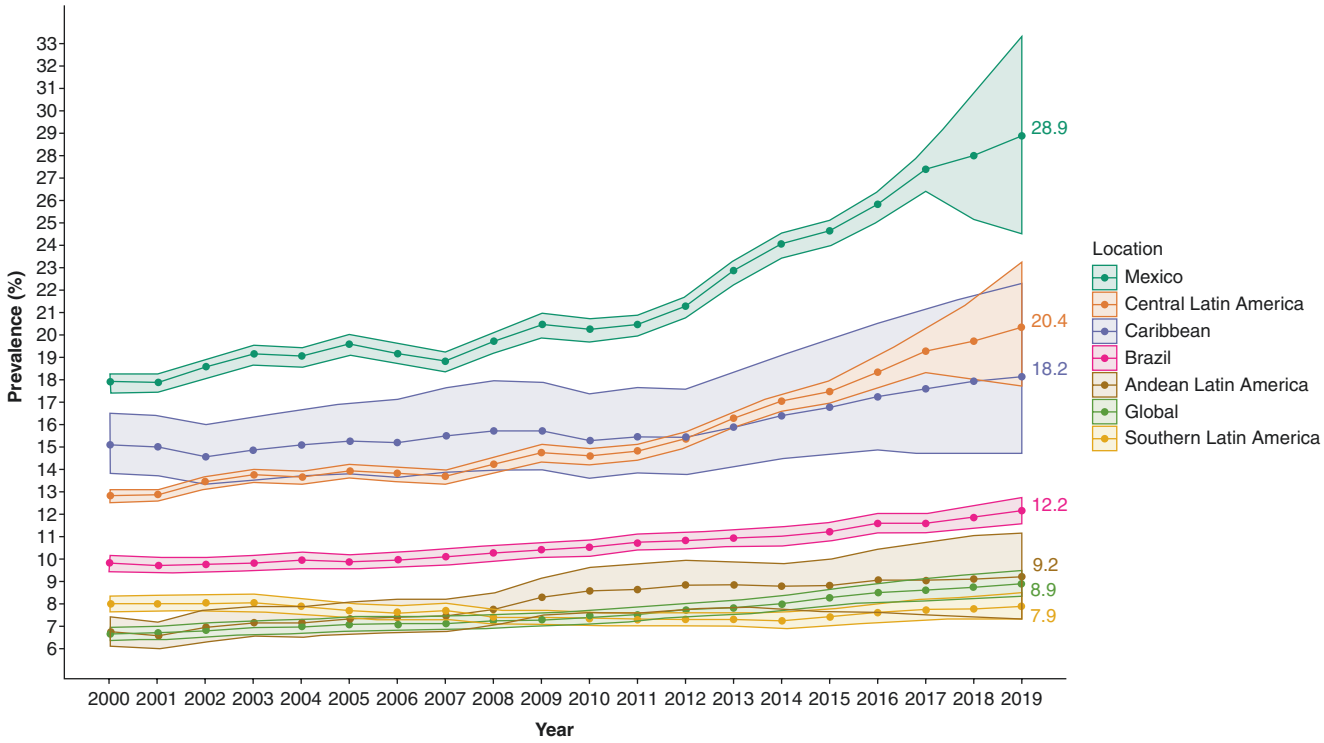

Fig. 18.2 Type 2 diabetes age-standardized mortality (per 100,000) in the Latin American and Caribbean sub-regions for 2000–2019, data from the Global Burden of Disease

[82]. Therefore, the high inequality observed in this region, within and between countries, needs to always be considered when planning public policies [83] which should be capable of reaching all those who can benefit from them.

Chronic Diabetes-Related Complications

Chronic diabetes-related complications can be divided into two major groups: microvascular (e.g. retinopathy, nephropathy and neuropathy) and macrovascular (e.g. cardiovascular diseases including coronary heart disease and stroke). The onset and prevalence of these chronic diabetes-related complications are closely related to metabolic control (e.g. optimal HbA1c levels), time since diabetes diagnosis and the synergic presence of other risk factors (e.g. smoking) and diseases (e.g. hypertension). While globally the mechanisms of these diabetes-related complications have been well defined along with prevention strategies and treatment [84–88], in Latin America and the Caribbean, quantifying the local burden and geographic distribution of these chronic diabetes-related complications is still an area of active research. Thereby, health authorities and practitioners still require a thorough understanding of the local epidemiology of chronic diabetes-related complications in order to set policies and interventions as well as to inform clinical practice guidelines for prevention and treatment.

Epidemiology: Microvascular

The large burden of microvascular diabetes-related chronic complications in Latin America and the Caribbean is likely linked to a twofold phenomenon: (a) on one hand, a large share of cases with type 2 diabetes is unaware of their diagnosis, particularly cases with a younger age at onset, who may have diabetes for longer without any proper treatment [89], and (b) a large number of cases live without adequate metabolic control, likely due to intrinsic deficiencies in access to treatment and disease monitoring throughout Latin America and the Caribbean [90]. These two factors interact and increase the likelihood not only of incident diabetes-related chronic complications but also increase the likelihood of disability related to improper long-term management of these conditions [77].

Despite the relevance of these microvascular diabetes-related chronic complications, currently there are no large-scale or multi-country prevalence studies of the epidemiology of chronic microvascular diabetes-related complications in Latin America and the Caribbean [91]. However, global analyses already suggest there is a large burden of microvascular complications in Latin America and the Caribbean [92]. For example, there are more years lived with disability due to diabetes-related lower extremity complications in Andean Latin America, the Caribbean and Central Latin America (second largest in the world) than the global average [92].

Evidence from community studies (i.e. not national and not in healthcare facilities) in Brazil revealed a diabetic retinopathy prevalence of 38% [93]; similarly, other studies in Brazil showed a 7% prevalence of diabetic retinopathy among people who are aware they had type 2 diabetes mellitus, and interestingly, 35% of those diagnosed with diabetic retinopathy did not know they had diabetes [94]; also in Brazil, of 533 patients with diabetes followed for retinopathy examination, 152 developed diabetes retinopathy or worsened their retinopathy over 9 years of follow-up in average [95]. In Ecuador, a community study showed that of 110 people with diabetes, 24% had peripheral arterial disease, 59% had peripheral neuropathy and 15% had both [96]. In the Republic of Suriname, a community study showed that among people with diabetes, 21% had diabetic retinopathy or maculopathy; furthermore, 8% had diabetic retinopathy at such a degree that would threaten their sight [97]. A study in Costa Rica found that diabetic retinopathy would be responsible for 6% of blindness cases [98]; following a similar methodology, researchers in Mexico found that diabetic retinopathy would explain 8% of blindness cases [99]. Another study in Mexico revealed that among people with diabetes, there was 15% prevalence of diabetic retinopathy; unfortunately, all these diabetic retinopathy cases had their sight threatened [100]. In Puerto Rico, the age-standardized incidence rate per 100,000 people with diabetes of end-stage renal disease was 196 in 2007 and 203 in 2010 [101, 102].

Studies in healthcare facilities also revealed heterogeneous results. An endeavour with inpatients in selected hospitals in nine countries in Latin America and the Caribbean showed that the prevalence of diabetic foot classified as Wagner 1 or above ranged from 3% in Bolivia to 13% in Chile [103]. In Argentina, the prevalence of diabetic foot in several healthcare centres with inpatient facilities was 14% [104]. In Brazil, a study with patients referred to specialized diabetes centres showed 46% retinopathy prevalence and 52% stage 1 nephropathy prevalence; regarding foot care, 18% had an active ulcer, 25% had a previous ulcer, and only 37% had foot without signs of risk [105]. Also in Brazil, a study in rural Basic Health Units with people with diabetes revealed that 63% of men and 36% of women had their feet foot with high risk of ulcers [106]. A study in Mexico based on administrative data informed that there were 100 major amputations per 100,000 people with diabetes in 2004, and this rate increased to 111 major amputations in 2013; these rates for minor amputations were 168 and 162 in 2004 and 2013, respectively [107]. In Peru, an analysis of a referral network for diabetic retinopathy showed 24% prevalence [108]; in addition, a surveillance programme in 18 hospitals in Peru informed that the most common complications were neuropathy (21%), diabetic foot (5%), nephropathy (3%) and retinopathy (2%) [109].

Epidemiology: Macrovascular

Cardiovascular diseases, with coronary heart disease and stroke at the top, are the leading cause of death in people with diabetes. Evidence suggests that people with diabetes have threefold risk of cardiovascular mortality (pooled relative risk = 2.7; 95% CI: 1.9–3.8) than people without diabetes [76]; apparently, this risk estimate is larger than that of other world regions [76]. A multi-country study in Latin America and the Caribbean with patients in healthcare centres gathering information from medical records showed that 7% also had coronary artery disease, 3% had myocardial infraction, 3% underwent percutaneous coronary intervention and 2% had stroke [110]. A lack of systematized information or a common registry of macrovascular complications in people with diabetes complicates the epidemiological characterization for this group of complications [111]. More data is required to evaluate specific risk factors, particularly those related to inequalities and intrinsic deficiencies in preventive care for people with diabetes, and which may inform preventive regimes and likely contribute to a reduction in the burden of cardiovascular disease in people with diabetes in Latin America and the Caribbean [112].

Final Remarks

In this section, we have summarized epidemiological evidence about chronic microvascular and macrovascular complications among people with diabetes in Latin America and the Caribbean. Evidence suggests that there is a large burden of these complications in Latin America and the Caribbean; nonetheless, much more research is needed to have a strong quantification of the burden of these complications at the national and sub-national levels in all countries of the region and to evaluate potential contributors of this phenomenon to inform future changes in public policy. A key factor to prevent or delay these complications is to reach optimal metabolic control. Unfortunately, metabolic control rates among people with diabetes are still low in Latin America and the Caribbean [113], and a large share of these patients is currently unaware of their diagnosis [113]. Ongoing and future work should strengthen the epidemiological and clinical evidence about these complications in the region while also securing optimal care for people with diabetes and timely detection of cases, particularly those with young disease onset so that they reach metabolic control and receive preventive care for these chronic complications.

Diabetes Interventions in Latin America and the Caribbean

Successful interventions are required to prevent and manage diabetes in Latin America, a region with significant increase in the number of people with this chronic condition. There are benefits achieved by preventive care among patients with diabetes. Although many of the interventions are focused on type 2 diabetes, some of them are being conducted enrolling type 1 diabetes cases.

Interventions in Type 1 Diabetes Mellitus

A limited number of interventions focused on type 1 diabetes have been evaluated in Latin America and the Caribbean. A randomized cluster trial was carried out to improve the quality of diabetes care in ten primary healthcare centres in Mexico using the chronic care model and the breakthrough series collaborative methodology [114], with an improvement in glycaemic control rates from 28% to 39%. Similarly, the proportion of patients achieving three or more quality improvement goals increased from 16% to 69%.

Two different programmes were also conducted in Brazil. One of them included a structured education programme on glycaemic control, knowledge and skills associated with diabetes care with workshops using the Dose Adjustment for Normal Eating (DAFNE) guidelines and subsequent reduction on HbA1c levels (20% in the first year and a further 11% reduction 8 months later) [115]. The second programme included an educational intervention tool and its potential impact on diabetes knowledge and behaviour of caregivers and school professionals. The intervention achieved the goal of informing and changing the behaviour of parents and school staff, improving the care provided to children with type 1 diabetes in schools [116].

Finally, in a pre-post evaluation, a coaching programme was implemented as part of the interdisciplinary care of individuals with type 1 diabetes in the Brazilian public health system, including weekly 60-min individual sessions for a total of eight sessions [117]. With ten patients in this pilot study, results suggested a reduction of HbA1c after 3 months and no further change at 6 months.

Interventions in Type 2 Diabetes Mellitus

Primary Prevention

There are relevant reasons why primary prevention of type 2 diabetes should be the dominant strategy for Latin American countries, mainly related to younger age group, female preponderance and high overweight and obesity prevalence. Interventions have been based on young subjects with impaired tolerance or fasting glucose, or with factors dramatically increasing the risk of developing type 2 diabetes, to improve lifestyle behaviours and potential risk factors. In an intervention in Colombia, using a three-arm randomized trial, two groups received early intensive lifestyle intervention compared to a control group (DEMOJUAN Project) [118]. One group received first a nutritional intervention for 6 months, physical activity intervention later for 6 months and then 12 months of a combined nutritional and physical intervention with specific goals, whereas the second group received only the physical activity intervention for 6 months plus the nutritional intervention for other 6 months. Despite of the 772 participants randomized and followed for 24 months, there was no significant difference between groups in the rates of reversion to normoglycaemia.

Nevertheless, two other clinical trials conducted in Brazil and enrolling subjects in high risk of type 2 diabetes have shown contrary results. One of them included group sessions twice per month and individual sessions once per month for 12 months and showed a decline in cholesterol, fasting and postprandial glycaemia and HbA1c [119]. The second study consisted of an interdisciplinary intervention with three visits plus an individual appointment with a dietitian and two-hour group sessions (four sessions in the first month, two sessions in the second month and one session monthly up to 9 months) [120]. This intervention reduced waist circumference, systolic and diastolic blood pressure as well as some domains in the 36-item Short Form Survey (SF-36).

Two quasi-experimental studies using a pre-post approach have showed benefits. One of the studies, conducted in Chile, assessed the results of an interdisciplinary pilot programme for overweight adults at risk of type 2 diabetes with reduction in body mass index, systolic and diastolic blood pressure, blood glucose, plasma insulin and HOMA [121]. The second study, carried out in Mexico, adapted the Diabetes Prevention Program with intensive sessions the first 3.5 months (weekly group and individual sessions) for lifestyle behaviour change and nutritional advice [122]. Intensity, however, lowered from 3.5 to 6 months, and only group sessions were done from month 6 to 12. The intervention group has significant weight loss, from 3 to 8 kg, at 6 months, but retention was only 40% at month 12.

Secondary and Tertiary Prevention

Different studies have been conducted in Latin America to address type 2 diabetes secondary and tertiary prevention. Many of the studies using a secondary prevention approach have been based on education programmes and, for instance, behavioural change. Thus, in Argentina, Gagliardino et al. conducted a randomized trial to assess four structured group education programmes (control, physician education, patient

education and both physician and patient education) using the Training Course for Physician and the Diabetes Structured Education Courses for People, with a follow-up of 3.5 years [123]. In this study, HbA1c decreased significantly from 4 to 10 mmol/mol by the end of the study, being the largest and more consistent reduction in the physician and patient group. Nevertheless, in Brazil, a 5-week educational group course (10 h), mainly focused on self-management, with reinforcements every 4 months for a total of 12 months, did not find differences between groups in HbA1c at 4, 8 and 12 months of follow-up [124].

In the case of behavioural change, in a clinical trial conducted in Trinidad and Tobago, the intervention consisted of identifying each patient's Stage of Change for managing their diabetes by diet, exercise and medications and using personalized, stage-specific care during consultations [125]. This intervention reduced HbA1c levels depending on the favourable movement to better stage of change in diet and exercise after 48 weeks. de Sousa et al. in Brazil used individual nutritional counselling every 2 weeks to reinforce and support dietary adherence and monitor caloric intake compared to such intervention with football training (3 weeks per week) [126]. A reduction in blood triglycerides, total cholesterol, LDL-cholesterol and VLDL-cholesterol was achieved in the football and dietary intervention during the 12 weeks of duration of the study. Similarly, West-Pollak et al. in Dominican Republic using a quasi-experimental design implemented a community-based lifestyle intervention programme developed by lay people perceived as leaders by community members and trained as healthcare champions [127]. Significant improvement in systolic, diastolic blood pressure and HbA1c levels was found after 6 months; however, only HbA1c improved after 1 year of follow-up.

In a randomized cluster trial in Mexico, a 13-week secondary prevention intervention, MetaSalud Diabetes, was implemented within the structure of a support group in government-run community health centres [128]. The programme consisted of two-hour participatory workshop-style session with educational information and empowerment-building discussions to promote long-term behavioural change. Participants' follow-up was carried for 12 months with reduction on cardiovascular disease risk at 3 months of follow-up in the intervention compared to the control group, but not significant change at month 12. In addition, diabetes distress was lower in the intervention group compared to controls.

In Costa Rica, using a quasi-experimental design, an educational community intervention for primary health care including type 2 diabetes patients, their family members and healthcare providers, was adapted to local conditions and patient's needs and implemented [129]. Providers improved their knowledge in diabetes prevention, treatment and education by a mean of 85%, whereas patients receiving the intervention improved their glycaemic control, without changes in body weight or lipid profile. In Mexico, an educative intervention comprising 12 modules with three 60-min sessions per week focused on self-monitoring, diet, exercise, complications, behaviour modification, self-care, family and sexuality, reduced fasting and postprandial glucose as well as HbA1c and cholesterol after 12 months [130]. Similarly, in Nicaragua, a prevention and self-management intervention delivery in interactive group format, including a one-on-one coaching component, for a total of 8 weeks, was conducted. This latter intervention reduced HbA1c from baseline to 3 months, and the greater reduction was found among those with HbA1c >7.5% at baseline [131].

On the other hand, two studies have reported findings using community health workers to deliver the intervention. A culturally adapted education intervention for type 2 diabetes patients was developed and implemented in rural communities in Guatemala using a one-group pretest post-test design and community health workers [132]. There was a significant decrease in the mean of HbA1c levels from baseline to 4 months of follow-up. In Brazil, salaried community health agents received a 32-h training in motivational interviewing-based counselling and behavioural action planning [133]. With support of booster training sessions, the community health agents used these skills in their regular monthly home visits over a 6-month period with patients with type 2 diabetes. Participants reported improvements in quality of diabetes care received, increase in physical activity levels, consumption of fruits and vegetables and medication adherence, with a subsequent reduction of HbA1c levels and improvement on LDL-cholesterol and triglycerides levels.

Some studies have utilized technology to improve the intervention to be implemented. In Peru, Lazo-Porras et al., using a clinical trial, conducted an education programme for preventing foot ulceration using reminders and foot-care promotion messages as SMS or automatic phone calls, and foot thermometry [134]. However, the addition of mHealth to foot thermometry was not effective in reducing the risk of ulceration after 18 months of follow-up. In Mexico, the Project Dulce model was evaluated using a randomized trial with three arms: control, educational sessions for self-management with, and without, wireless technology [135]. Such educational programme included eight 2-h weekly sessions led by peer diabetes partners during the first 2 months of the intervention, with a subsequent drop in HbA1c levels from baseline to month 10 of the intervention groups compared to the control, being greater among those using wireless. In addition, a single group, pre-post study was conducted to evaluate the feasibility and potential impact of an interactive voice response programme using a cloud-computing model to improve diabetes management in Honduras [136].

After 6 weeks, participants reported that because of the programme, they improved diabetes management, including glycaemic control or foot care; there was also a reduction of HbA1c levels.

One study in Latin America tried to improve glycaemic control by using monetary incentives. This three-arm randomized clinical trial was a small pilot conducted in a tertiary level public hospital in Peru [137]. All participants received diabetes education and tailored goal setting for weight and HbA1c levels and assigned to one of the three arms: individual incentives, mixed incentives—altruism and mixed incentives—cooperation. After 3 months, participants in all three arms showed reduction in weight and HbA1c level.

From the tertiary prevention perspective, only one randomized clinical trial, conducted in Argentina and Chile, was carried out comparing percutaneous transluminal coronary angioplasty versus stent among patients with type 2 diabetes to reduce the incidence of angiographic restenosis, with no differences between group after 30 days and 9 months of follow-up [138].

Final Remarks

As diabetes increases in Latin American and the Caribbean region, innovative and effective interventions are required to improve health outcomes. In this section, we summarized several initiatives in Latin American and the Caribbean countries that focused mainly on diabetes risk reduction and diabetes management, some of them showing promising results. Evidence supports than education programs may be relevant but not enough to improve glycaemic control. Thus, a multidisciplinary approach may be efficacious for diabetes management, including community health workers, using a self-management approach, and including the use of technology.

Implementation Science for Type 2 Diabetes Mellitus in Latin America and the Caribbean

Implementation science is usually defined as "the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, hence, to improve the quality and effectiveness of health services and care" [139], and it has the objective to close the know-do gap, the differences between what we know works and what we do, by addressing barriers and facilitators to the uptake of interventions [140].

For diabetes, this science is essential due to the complexity of this chronic condition in terms of the different levels of influence and the multiple interactions between them (individual level, family, community, health system, environment and policies) [141, 142]. In that sense, it is relevant to translate the knowledge to daily practice and to understand how the intervention was implemented in the field [143, 144]. Latin America had previous experiences implementing context-adapted interventions, and they will be explained as case studies. Additionally, using implementation science, it is possible to identify some barriers and facilitators to achieve an adequate management, and this information will be presented too.

Examples of Successful Experiences

Case 1: The VIDA Project

The aim of this project was to improve the quality of care in people with diabetes at the primary healthcare level in Mexico [114]. The intervention was a quality improvement project that included three learning sessions for the primary healthcare teams and personnel from the local hospital. The chronic care model was used to let health personnel to identify their problems to provide care, and the "plan, do, study, act" was used to co-develop solutions. Also, they received training in patient's education, foot care and diabetes management in primary care.

The study was a pre-post design conducted in the state of Veracruz, and the intervention was delivered in ten centres with ten other centres receiving usual care. Quality improvement was measured by changes in the proportion of patients achieving the diabetes care goals such as metabolic control (HbA1c <7%), total cholesterol <200 mg/dL, blood pressure <140/90 and to have received foot and eye examination.

After 18 months of study, they found an increase in the proportion of the management of three or more treatment goals in the intervention group from 16% to 69%, whereas the usual care group did not present such difference. The proportion of those who achieved the blood pressure goal did not present a difference in neither of the groups.

Also, patients that participated in the education sessions provided feedback and mentioned that they found the support groups very useful to increase physical activity and they indicated that activities need to be tailored to different types of patients. Additionally, the health personnel selected objectives for improvement activities, and the implementation of the "plan, do, study, act" was successful.

Case 2: The Meta Salud Diabetes Implementation Study

This project evaluated the effectiveness of Meta Salud Diabetes to reduce cardiovascular risk [128]. They used a clustered randomized trial in urban and rural areas from Sonora, Mexico. The intervention included 13 sessions of

two hours each in support groups (Grupo de Ayuda Mutua—GAM) to provide education and hold empowerment discussion and also included blood pressure and glucose monitoring, games and the design of a physical activity routine. The intervention was delivery by diverse health professionals trained to guide the session. The comparison group was participants of the usual care activities of the GAM that includes sessions with invited speakers to provide general information about diabetes. The outcome was cardiovascular disease risk using a score, and the follow-up was at month 3 (at the end of the intervention) and at 12 months (to measure sustainability).

Cardiovascular disease risk was lower in the intervention arm in comparison with the control arm at 3 months, but the difference was not maintained at 12 months. The effect was modified by gender (having a positive effect in male and not in female at 3 and 12 months) and baseline HbA1c (having a positive effect in people with HbA1c <8 and not in those with higher HbA1c).

The project also included a qualitative study to explore the willingness of the staff, their capacity and the resources available to implement Meta Salud Diabetes within the existing GAM structure. Some characteristics were identified that could boost the adoption of the intervention such as management, staffing and local environment. Barriers included the absence of standardized training and capacity building in chronic disease and health promotion, a need for supervision and feedback to the programme, scarce medical supplies and lack of interdisciplinary support. Modifications are possible to adapt the intervention to realities of the health centre environment [145].

Case 3: Combined Diabetes Prevention and Disease Self-Management Intervention for Nicaraguan Ethnic Minorities: A Pilot Study

The study assessed the feasibility, acceptability and preliminary efficacy of a community-based participatory research [131]. A pilot study was conducted in two groups considered ethnic minorities from Nicaragua (Miskitos and Creoles). The setting was a rural area, and the intervention was developed in collaboration with local church and community leaders to prevent and promote self-management of diabetes and complement with input from community nurses and physicians. The intervention included two main components: (a) group sessions led by a nurse with motivational interview and goal settings for diet and exercise (eight sessions of one hour) and also (b) one-on-one meetings to individualized diabetes prevention or promote self-management (four sessions of 30 min).

The pilot study intervened in 42 participants and follow-up 33 of them. The mean HbA1c improves from 8.8% to 8.3% in 3 months, and the impact was slightly higher in those that had a higher HbA1c at baseline (from 9.7% to 9.0%). Also, the intervention was acceptable, and the feasibility was good with successful research capacity building and achievement of sampling goals.

Other implementation studies can be found in the literature [146] and included diverse intervention approaches, e.g. one study evaluated the challenges of implementing a clinical practice guideline in public hospitals in Mexico [147]; other study in rural Guatemala implemented a quality improvement strategy at the household, clinic and institutional level [148]; also, a study in Brazil evaluated the introduction of an application for decision system support used by health professionals. It included clinical evaluations and blood glucose measurements and generated specific recommendations based on the data provided [149]; finally, an intervention to prevent diabetic foot ulcers through the implementation of foot thermometry and mHealth achieved good adherence to temperature measurements, but the intervention was not superior to the control arm (foot thermometry alone) [134].

A recent systematic review identified the barriers and facilitators to achieve a successful management of type 2 diabetes using the Theoretical Domain Framework [150]. They included 60 studies and found that 54 studies (90%) identified factors related to the environmental context and resources. Challenges due to "social influences" (40 studies) such as lack of support from family members were found. Additionally, clinician's paternalistic attitudes as well as other negative attitudes (37 studies) were frequently addressed. Other barriers were related to the patient's beliefs (25 studies) that end up in low patients' trust in the treatment and/or physician and the use of alternative therapies.

Know-Do-Gaps for Type 1 Diabetes Mellitus

In the case of type 1 diabetes, guidelines have identified key priorities to improve type 1 diabetes care such as education and information, blood glucose management, insulin therapy, awareness of hypoglycaemia and detection and management of psychological and social issues, among others [151, 152].

There are no implementation science studies conducted in Latin America for type 1 diabetes. However, we will describe one model to integrate implementation science into paediatrics psychology developed in the USA and the implementation of a social support event for children with type 1 diabetes and their families conducted in the USA. These examples might help the reader grasp important concepts related to implementation science and might also motivate them to use implementation science methods within their research.

Price et al. propose a model for integrating implementation science into paediatric psychology for type 1 diabetes [153]. The model has four steps: (a) identifying the gap of psychological management of patients with type 1 diabetes, (b) identifying barriers and facilitators using the Consolidated Framework for Implementation Research (CFIR) framework

[154], (c) developing implementation strategies using those identified in The Expert Recommendations for Implementing Change (ERIC) project [155], and (d) evaluating implementation outcomes as acceptability.

Education and psychoeducation interventions have proven effective to reduce HbA1c and increase children's self-efficacy to manage type 1 diabetes [156]. However, Price et al. identified a gap in management of psychological issues in patients with type 1 diabetes, as they cite, only 18% of families with these patients attended at least one psychology visit within a 2-year period in Boston, USA [157]. He proposed some barriers using the CFIR framework: outer setting (patient needs, patient and family perspectives, stigma associated with psychological care and insurance coverage), inner setting (staffing and space), characteristics of the individuals (lack of awareness of the effectiveness of paediatric psychology care among patients, families, providers and payers), intervention characteristics (length and number of sessions) and process (need to have a plan for implementing paediatric psychology care). Based on this information, they expect to develop targeted implementation strategies to then test them.

It is important to note that the proposed model uses implementation science methods that could be used in different contexts, including Latin America. Thus, following the proposed four steps of the model could help researchers develop a clear research plan from the identification of a research gap to the development and evaluation of implementation strategies.

Shea et al. conducted a study to assess the implementation of the "Diabetes Day" [158], a social support event for children with type 1 diabetes and their families, as they noticed that only 25–50% of the families who confirmed participation actually assisted to the event. Shea used the Rogers's diffusion of innovation theory to assess the dissemination and acceptance of the "Diabetes Day" event. This framework was used to evaluate each step of the event, and information on programme success, barriers to participation and suggestions for future sessions were collected through surveys to families and healthcare providers. Then, the staff planned the next session meeting children and parents' expectations such as including outdoors activities in the summer when children will be out of school. Additionally, to improve recruitment of families, flyers were designed and pasted in the hospital, and the "Diabetes Day" information was added to the discharge sheets that providers use during patient visits.

Access to Treatment

Hypoglycaemic Medication

The access to hypoglycaemic medication is unequal around the world with greater disadvantage for low- and middle-income countries in the Latin American Region. According to an International Diabetes Federation survey which included 13 countries of South America and the Caribbean Region, metformin was available in 65% of middle-income and only in 20% of low-income countries and sulfonylureas in 46% and 10%, respectively [159]. Those numbers are far from the target of 80% availability of essential medicines for the prevention and treatment of diabetes recommended by the World Health Organization (WHO) in the Global Action Plan for the prevention and control of non-communicable diseases [160].

The survey methodology proposed by the World Health Organization and Health Action International (WHO/HAI) [161] to assess price, availability and affordability was applied in different countries in Latin America. For instance, Brazil, El Salvador and Peru as representative countries of South America reported a mean availability of glibenclamide 5 mg/tab of 79% in the public sector and 90% in the private sector, which are higher results than the result from Africa, Asia, the Eastern Mediterranean region and the Western Pacific but lower than the European region [142]. In terms of affordability, to supply a treatment for 30 days with glibenclamide 5 mg/tab, the lowest-paid unskilled government worker has to spend 1.6 day's wage to acquire a generic brand and 4.5 day's wage for an originator brand [162]. A medicine is considered affordable when the lowest-paid unskilled government worker spends less than 1 day's wage to pay for a regular treatment [161]. Data compiled from different countries showed that the availability of metformin 850 mg/tab in the public sector decreased in the following order: Colombia > Mexico > Ecuador > Bolivia > Brazil, while for the affordability of generic brand in the private sector decrease as follows: Bolivia > Ecuador > Mexico > Braz il > Colombia [163]. It is important to note that the price also varies depending on the brand; for example, in Peru, they found that the median price of metformin 850 mg/tab in private pharmacies was 0.12 USD for a generic brand and 0.53 USD for an originator brand [164]. This price difference may in part from the large number of generic manufacturers in the country and the pricing regulations.

It is true that in some countries, such as México, Brazil, Colombia, Ecuador and Peru, hypoglycaemic drugs are provided free of charge with public insurance; nevertheless, the low availability in the public sector force patients to go to the private sector where the price may be up to ten times higher generating high out-of-pocket expenses with significant impact on the most disadvantaged ones [162–164]. For example, in Mexico, it was reported that even though older adults have public insurance, they faced out-of-pocket expenses, and these are greater among rural populations, mainly because some medicines are not covered by the public insurance [165, 166]. Besides the public insurance, other factors associated with limited access to medicines for chronic conditions in Latin American countries include people who live in rural areas or with less proximity to health-

care facilities; where the household head is retired or belong to an ethnic minority; being older than 65 years; and worse economic household level and with equal or less than elementary education [167].

There are also positive initiatives, for example, the government of Brazil implemented subsidy policies for essential medicines for hypertension and diabetes (the Farmácia Popular Program) that in 2004 started just with public pharmacies but in 2006 was expanded to private ones. This programme improved the availability of essential medicines and the affordability but also increased the number of dispensations and sales of generic medicines [168]; unfortunately, an adequate access to medicines did not assure adherence to pharmacological treatment [169].

Insulin

The expenditure for insulin in Latin American and the Caribbean is estimated between USD 6 and USD 11 billion, almost twice the expenditure for oral antidiabetics [170]. In this region, between 13% and 36% patients with type 2 diabetes use insulin, either alone or in combination with oral antidiabetic drugs, being the most prescribed insulin the human intermediate-acting or isophane [41, 171].

Using the WHO/HAI methodology [161], a study in 2007 in Brazil reported an availability of 40% for regular insulin and 50% for isophane insulin and an affordability of 2.8 day's wage for isophane insulin in the private sector [172]. Another study with the same methodology in 2019 showed that the availability of isophane insulin improved to 80% in the public sector, while its affordability in the private sector remained stable [173]. From 2006, the Brazilian federal government provided free of charge human insulins (regular and isophane) in the public sector and through patient's co-payment with government subsidy in the private sector. In 2011, the programme "Health has no Price" (Saúde Não Tem Preço, in Portuguese) established a partnership with private pharmacies to provide regular and isophane insulin free of charge, with a government reimbursement. In the first 12 months of "Health has no price", the number of units dispensed in private pharmacies increased by 97% for regular insulin and 78% for isophane insulin, while the dispensing of fixed-dose combination (regular/isophane) decreased which may indicate a preference for using medicines provided by the programme [174]. The different efforts of the Brazilian government generated an investment of USD 1027 billion between 2009 and 2017 and benefited thousands of patients; however, it also implied important expenses in reimbursement [175].

Regular and isophane insulins are listed in the WHO model list of essential medicines [176] as well as in the National List of Latin American countries; this denomination facilitates the procurement through public tendering at national level which take advantage of economies of scale and achieve lower prices. The no inclusion of analogue insulins in National List of Medicines prevents their acquisition through tendering in some countries such as Peru and Brazil, but this does not hinder their existence in public hospital since analogue insulins may be procured at a local level [164, 175]. This increases inequity because these analogue insulins are only available for a small proportion of the population, and the expenses in their procurement are high. For example, in Peru, it was found that 10% of public hospitals have analogues, but their acquisition price (USD 57) represented almost ten times the acquisition price of human insulins (~USD 4) [164].

Price differences not only occur between human and analogues insulins; there is also important price variation between originator brand and biosimilar [173]. Price regulation led to less variability in markups, but not necessarily lower prices [177]. For example, in Peru, ingredients for the manufacture of medicines for diabetes and the medicines itself are free of import taxes, but the price of the same type of insulin may vary between USD 49 and USD 107 [164].

Cardiovascular Treatment in People with Diabetes

It is described that antihypertensive treatment achieves cardiovascular risk reduction if treatment starts as soon as possible and the goals are reached soon [178]. In relation to lipid-lowering medication, a systematic review and meta-analysis published in 2010 explored the effect of statin use vs. placebo and more intensive lowering of LDL cholesterol regimen against less intense regimen in major cardiovascular events. The study found that comparing statin/more intense regimen vs. control/less intense regimen for type 1 diabetes, the effect (rate ratios) on first major vascular event (first occurrence of any major coronary event, coronary revascularization or stroke) per 1.0 mmol/L reduction in LDL cholesterol was 0.77 (95% CI: 0.58–1.01) including 337 events, whereas for type 2 diabetes, it was 0.80 (95% CI: 0.74–0.86) including 5414 events [179].

However, there is no pooled data from Latin America to know the proportion of people with diabetes that achieve the blood pressure or lipid lowering goals as well as the percentage of people who have access to their medication. Only some studies usually conducted within the health system setting explored these data and found that between 25% and 67% of patients reached the goals for blood pressure (considering different definitions) and between 12% and 52% reached the goals for LDL cholesterol [180].

In terms of access to cardiovascular medication, there is data from the PURE study that evaluated availability and

Table 18.2 Availability and affordability of four cardiovascular medicines by country income group

	Availability of four cardiovascular medicines		Unaffordable for population (%)
	Urban	Rural	
High-income countries	61 (95%)	27 (90%)	0.14
Upper middle-income countries	53 (80%)	43 (73%)	25
Lower middle-income countries	69 (62%)	42 (37%)	33
Low-income countries, excluding India	8 (25%)	1 (3%)	60

affordability of 4 cardiovascular disease medicines including aspirin, β-blockers, angiotensin-converting enzyme inhibitors, and statins in 18 countries (4 from Latin America); and they found differences by income status of the countries [181]; and differences between urban and rural areas were identified as well (Table 18.2). Also, affordability of the four cardiovascular medicines were defined if the cost was less than 20% of household capacity-to-pay, and Chile and Brazil were under the 20% cut-off point, whereas Colombia and Argentina were around 45% [181].

Prediction Tools

Countries within the Latin America and the Caribbean region have high rates of patients with undiagnosed diabetes, and many of whom do not have adequate glycaemic control and are at high risk of acute metabolic events and chronic micro- and macrovascular complications [112]. In an effort to promote prompt identification of cases with suspected type 2 diabetes, predictive modelling approaches have been proposed as triage or screening methods to identify patients who are likely to have undiagnosed diabetes and would benefit most from additional screening methods including serial fasting glucose measurements, oral glucose tolerance tests or HbA1c measurements in an effort to improve resource allocation in rural or limited resource settings [182]. In this section, we will discuss evidence regarding the utility of diagnostic and prognostic tools for type 2 diabetes and diabetes-related complications.

Diagnostic and Prognostic

Given some described differences in onset, progression and treatment response of patients with type 2 diabetes in Latin America and the Caribbean, there is a need for the development of predictive modelling approaches which incorporate metabolic particularities of these populations [112, 183]. To be useful, predictive models for type 2 diabetes need to satisfy certain requirements including: (1) They need to be simple and widely applicable to justify its use instead of a simple (but arguably invasive) fasting glucose measurement; (2) need to consider items which make diabetes unique in the region, including earlier age at disease onset, lower degree of obesity required compared to similar ethnicities and unique genetic susceptibility for development of diabetes independent of additional risk factors; and (3) need to show that its use could lead to improved outcomes or more precise public policy planning. To date, no single model has shown to be cost-effective to be widely recommended as a tool to promote effective screening and diagnosis of diabetes in the region [183, 184].

A 2019 systematic review summarized at least five diagnostic tools which have been developed in different countries, which have primarily focused on prevalent but previously undiagnosed diabetes cases in Brazil, Mexico and Peru [183]. These models are driven primarily by consideration of age, obesity traits (assessed by body mass index and waist circumference), family history of diabetes and secondary predictors including sex, blood pressure levels and individual components of the metabolic syndrome, which have had limited assessment regarding its incidence in countries outside of Mexico [185]. Additional modelling approaches not considered in the systematic review include two incidence models for prediction of 3-year risk of diabetes mellitus in Mexico based on convenience sampling and an additional model based on the population-based ENSANUT, with similar characteristics to the tools appraised in the systematic review [186–188]. Finally, models developed in other populations such as FINDRISK have been externally validated in the region but have failed to show adequate calibration or be cost-effective in comparison to simpler screening techniques [184, 187]. Additionally, few of these diagnostic and prognostic models have been externally validated, and none have been validated for all countries within the Latin America and the Caribbean region, opening up opportunities for further research in validation studies [183].

A main limitation of current modelling approaches includes that ascertainment of the outcomes is standardized using fasting glucose measurements, with only one model in Peru assessing the outcome based on an oral glucose tolerance test [183, 184]. This may underestimate the true prevalence of potentially undiagnosed diabetes, given the low concordance between fasting glucose levels, impaired oral glucose tolerance and abnormal HbA1c levels [189, 190]. In addition to these concerns, models developed for a specific population in the region may not have external validity for other countries. To mitigate this, modelling approaches should consider including regional predictors or may need to incorporate habits or region-specific traits as candidate pre-

dictors which may be applicable for the overall region in order to tailor predictions to better represent the epidemiologic landscape of diabetes. As of the time of this writing, no model can be considered to be widely applicable for the region, and most models have shown limited performance as screening tools in the population. Models for incident type 2 diabetes have not been developed using population-based samples, opening a need for the development of prospective development and validation studies in the region [183, 184]. These models may offer a unique opportunity to inform preventive regimes aimed at ameliorating the impact of specific risk factors on diabetes incidence, which may have better long-term public health implications beyond the individual benefits usually expected for predictive modelling [182].

Diabetes-Related Complications

As commented in the preceding sections, the epidemiology of chronic diabetes-related microvascular and macrovascular complications for countries in the Latin America and the Caribbean region is incompletely characterized, with no systematized approaches to describe at a larger scale its prevalence or incidence or to characterize unique risk factors for this region [112]. Given these limitations in the characterization of chronic micro- and macrovascular diabetes-related complications, predictive modelling for prevalent or incident chronic complications is scarce [191]. Few approaches have dealt with prevalent diabetic retinopathy, diabetic kidney disease, diabetic neuropathy and chronic diabetes-related cardiovascular complications, with only one study incorporating omics technologies as complementary in prediction to traditional measures and risk factors for diabetic kidney disease [192–195]. To be useful, models for diabetes-related complications need to show superiority compared to commonly used predictors including HbA1c and years of diabetes exposure to be clinically useful. Despite the existence of models for identification of chronic complications in selected populations, no model has been developed for prognosis of incident complications at national scales across the region besides few studies assessing convenience and non-population-based samples to varying degrees of success [191].

To be cost-effective and potentially clinically applicable, further modelling approaches for chronic diabetes complications in Latin America should consider (1) evaluating ethnic-specific traits which may increase risk of developing chronic micro- or macrovascular complications or decrease age of onset or at lower HbA1c levels, (2) demonstrating its superior performance compared to commonly used predictors including HbA1c and years of diabetes exposure and (3) showing that its implementation either at individual of population level has the potential to lead to improvements in diabetes-related outcomes, beyond its informative nature. Current approaches have not been externally validated across the region, rigorously tested and must be considered at moderate to high risk of bias if implemented outside of its origin population. Therefore, prospective and planned modelling approaches need to consider that low-cost models need to be developed if they are expected to be used for diagnosis, prognosis or follow-up for cases with type 2 diabetes in Latin America and the Caribbean.

New Research Trends

Population Health

Diabetes is a complex disease which needs synergic work whereby practitioners and public health officers work together, while the former deliver high-quality care to patients, and the latter provide good understanding of the epidemiology and design policies and interventions for primary (i.e. to prevent or delay diabetes onset), secondary (i.e. to secure effective treatment) and tertiary prevention (i.e. to improve health and well-being after a complication has occurred). Research in population health related to diabetes could provide evidence to inform these three stages of care.

A study in Brazil showed that in 2013, 9% of all deaths were attributable to diabetes when diabetes was self-reported (i.e. people aware they had diabetes) [196]; when unknown diabetes was considered, this figure rose to 14% [196]; conversely, when diabetes mortality was ascertained from death certificates (i.e. underlying cause of death), this figure was 5% (and 10% when diabetes was anywhere in the death certificate) [196]. These findings imply that diabetes mortality based on death certificates may underestimate the real mortality burden attributable to diabetes. This could have a few pragmatic implications: (a) national and regional health authorities in Latin America and the Caribbean could agree on how to quantify the mortality attributable to diabetes and provide tools and guidelines for that; (b) there is a need to improve death certificate registration when the underlying cause may be diabetes; and (c) improving prompt identification of cases with type 2 diabetes may have relevant implications not only for short- and long-term disease monitoring but also for quantifying the true impact of the disease and required policy changes.

A work in Andean Latin America (Bolivia, Ecuador and Peru) computed the number of diabetes cases attributable to high body mass index since 1980 [65]. They showed that, during the study period, the number of diabetes cases attributable to class I obesity increased the most followed by those attributed to class II obesity [65]. Moreover, there were substantial differences between countries [65]. From these findings, one could gather that reducing obesity is paramount

and that even class II obesity is now found with higher frequency. To reduce the impact of obesity on diabetes incidence, a combination of medical and public health interventions would require (a) medical interventions to provide treatment and counselling to people who already have obesity; (b) public health (population-wide) interventions so that the mean body mass index in the population would reduce; and (c) to evaluate public policies related to promotion of healthier lifestyles beyond weight loss to reduce overall metabolic burden. The fact that there were differences among three countries with similar epidemiological background is also interesting and calls to study all countries to find country-specific patterns of diabetes prevalence and incidence, or similarities between countries which could address the heterogeneity of type 2 diabetes. This could help to find countries where similar interventions can be delivered with the support from regional or global health organizations.

Novel Analytic Approaches

Novel research and analytical approaches are developed every day, and they can be incorporated in our research toolbox to provide answers to relevant research questions in the fields of clinical medicine and public health in Latin America and the Caribbean. A main goal of data-driven methods in diabetes is to address the high heterogeneity of diabetes by providing an analytic framework which builds from advances in knowledge regarding the pathophysiology of type 2 diabetes, novel insights into disease monitoring and follow-up and incorporation of improved treatment regimes.

As discussed above, risk prediction tools are useful for risk stratification and to inform treatment allocation and clinical management. Similarly, data-driven clustering of people with diabetes can deliver equivalent information by finding groups of patients with similar characteristics, with similar response to a given treatment, or that would have the same (or similar) disease progression. Research outside Latin America and the Caribbean has shown that clustering patients with metabolic and clinical characteristics could be useful in identifying groups for risk stratification and treatment response [197–199]. One study in Mexico proved that this approach would also be feasible in Latin America and the Caribbean, with relevant implications for clinical management of patients with diabetes [193]. For example, patients in the same diabetes cluster could receive similar treatment, or patients in the same cluster of disease progression could receive similar treatment to avoid or delay unfavourable outcomes. These clustering methods, which aim to systematize previously identified differences in the pathophysiology and evolution of type 2 diabetes at an individual level, may have relevant implications for the advancement of personalized medicine; however, these individualized approaches may fail when applied to large-scale epidemiological efforts because they do not adapt to the population of origin. At the population level, another study in Latin America and the Caribbean analysed national surveys and found cluster of patients with shared profiles; they also described the frequency of these clusters in nine countries from this region [200]. This information at the population level could be used to plan interventions or policies. For example, a cluster had people with diabetes and high blood pressure; in places where this was the most frequent cluster, they should secure effective cardiovascular treatment for people with diabetes. Likewise, in places where the most frequent cluster was that with diabetics with high body mass index or waist circumference, they should secure effective weight management for patients with diabetes. These two approaches—clusters of patients and populations—are complementary and could create a synergistic approach to both further treatments tailored for individual patient characteristics while pushing for population-level interventions informed by specific traits of the population.

Other research innovations include deep learning, a group of techniques within the remit of artificial intelligence. Deep learning can be used to analyse images like photos. In the global literature, there are several examples in which deep learning has been used to classify (i.e. diagnose) images of diabetic retinopathy with good accuracy [201]. Deep learning has also been used for diabetes diagnosis and glucose monitoring based on sequential follow-up glucose measurements [201]. For these analytical tools to perform, accurately good and large data sources are needed. Latin America and the Caribbean should improve their data collection standards and availability, particularly of administrative data. This way, researchers can explode these sources to inform decisions, interventions and clinical guidelines. Electronic health records are useful source of data, though these are still not available in all countries in the region largely due to technical difficulties of lack of systematization of these approaches in individual countries. Efforts are needed to strengthen these and other sources of administrative data.

Finally, longitudinal studies are required to inform different aspects of disease progression, monitoring and prognosis. Since ethnic-specific differences in the pathophysiology of type 2 diabetes have been reported for countries within the Latin America and the Caribbean region, many commonly accepted paradigms of treatment, prevention and monitoring need to be confirmed for feasibility and wider applicability in these populations, calling for studies conducted in the region to validate findings or adapt them to fit the reality of the region to maximize its potential impact. This will require a conjoined effort between many research teams and will likely require several years to realize, but its utility in advancing the understanding of diabetes in the region makes these efforts of uttermost importance.

Multiple-Choice Questions

1. Regarding genetic traits known to be a risk for increased incidence of type 1 diabetes, please choose the incorrect statement.
   (a) HLA-DQ in Mexico and Uruguay
   (b) RNASEH1 in Colombia
   (c) CD226 in Argentina and Colombia
   (d) DQ8 in Brazil
   (e) **PD-L1 and PD-L2 in Peru**
2. In relation to other world regions and regarding the age-adjusted comparative diabetes prevalence, South America and Central America rank:
   (a) 1st (out of seven world regions considered)
   (b) 2nd (out of seven world regions considered)
   (c) **5th (out of seven world regions considered)**
   (d) 4th (out of seven world regions considered)
   (e) 3rd (out of seven world regions considered)
3. The highest and lowest proportions of undiagnosed diabetes appear to be in ___ and ___:
   (a) **Haiti and Chile**
   (b) Peru and Colombia
   (c) Panama and Chile
   (d) Haiti and Costa Rica
   (e) Nicaragua and Mexico
4. In 2019 in Latin America, the two countries with the highest absolute number of people living with diabetes were:
   (a) **Brazil and Mexico**
   (b) Argentina and Mexico
   (c) Mexico and Chile
   (d) Panama and Mexico
   (e) Brazil and Peru
5. In Latin America, the risk of cardiovascular mortality in people with type 2 diabetes (compared with diabetes-free people) is:
   (a) 0.5-fold
   (b) 1.7-fold
   (c) **2.7-fold**
   (d) 3.7-fold
   (e) 4.7-fold
6. Regarding the VIDA Project, choose the incorrect statement.
   (a) **Blood pressure treatment goals were improved after the intervention.**
   (b) The outcomes were measured after 18 months.
   (c) Study design: pre-post.
   (d) Metabolic control was defined as HbA1c <7%.
   (e) The total cholesterol goal was <200 mg/dL.
7. The research on implementation science for type 1 diabetes in Latin America have addressed:
   (a) Timely diagnosis.
   (b) Treatment access.
   (c) Treatment adherence.
   (d) **There are no implementation science studies conducted in Latin America for type 1 diabetes in particular.**
   (e) Metabolic control.
8. The expenditure for insulin in Latin America and the Caribbean is estimated at:
   (a) **Between USD 6 and USD 11 billion**
   (b) Between USD 6 and USD 11 million
   (c) Between USD 5 and USD 10 billion
   (d) Between USD 5 and USD 10 million
   (e) Between USD 7 and USD 12 billion
9. To be useful, predictive models for type 2 diabetes need to satisfy certain requirements; select the correct statement.
   (a) Simple and widely applicable.
   (b) It considers unique features of diabetes in the region along with general risk factors.
   (c) It leads to better outcomes and more precise public police planning.
   (d) (a) and (c).
   (e) **(a), (b) and (c).**
10. Regarding diabetes incidence in Latin America, choose the incorrect statement.
   (a) PERUDIAB estimated the diabetes incidence in urban areas of Peru as 19.5 per 1000.
   (b) **In Peru, the PERU MIGRANT study found a higher incidence that the PERUDIAB study.**
   (c) The ELSA-Brazil cohort reported a diabetes incidence estimate of 2.0 per 100.
   (d) In Mexico, the highest incidence has been found in the age group 50–59.
   (e) In Mexico, the incidence in men 50–59 was 23 per 1000.

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Diabetes Management in the United States

19

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Introduction

Prevalence and Cost Burdens

In the United States (USA), diabetes affects approximately 11% of the population, and in 2020, this equated to an estimated 34.2 million Americans with diabetes [1]. Type 2 or insulin-independent diabetes accounts for the majority (~90 to 95%) of cases in the United States [2]. Furthermore, approximately one-third of US adults have prediabetes, an identifiable precursor phase in which blood glucose levels are above normal but not yet in the diagnostic range for diabetes, and one's risk of developing type 2 diabetes increases 5- to 12-fold [3].

The diabetes epidemic has evolved considerably over the last quarter century. At every counting, the growth in prevalence and absolute numbers of people with diabetes has far exceeded statistical projections. Further, over time, larger proportions of those affected by diabetes are people of minority race/ethnicities and from lower socioeconomic backgrounds, and onset and first diagnosis appear to be younger than in decades past [4].

Diabetes is associated with billions of dollars in health expenditures and lost productivity [5–7]. Using a compilation of national data sources, diagnosed and undiagnosed diabetes accounted for over $400 billion in economic burden, which includes medical expenditures and reduced labor force participation, early mortality, and lower productivity in 2017. As a result, diabetes is one of the leading contributors to rising healthcare costs in the United States [8, 9].

Health Impacts

Type 2 diabetes typically develops over many years. The slow progression and lack of symptoms in the early stages of disease often delay requests for a screening test, preventive care, and/or medical attention. Other issues, such as lack of insurance or access to timely preventive care, may compound these delays. As such, even in high-income country settings like the United States, approximately 21% of people with diabetes are not aware of their diagnosis [1]. This is problematic as the pathophysiology of diabetes and its impacts on organs continues unabated despite the individual's awareness (or lack thereof) of their glycemic status.

The health impacts of diabetes vary by the type of disease. Type 1 or insulin-dependent diabetes, which accounts for about 5% of cases in the United States, is more commonly associated with acute fluctuations in blood sugar levels. Episodes of severe acute hyperglycemia (e.g., diabetic ketoacidosis [DKA] [10] and hyperosmolar nonketotic coma) or, conversely, severe hypoglycemia most often require immediate medical management. When treated in a timely and appropriate manner, the mortality from acute hyperglycemic episodes such as DKA is extremely low in the United States [11, 12]. Individual patient (e.g., age, additional comorbidities) and resource (e.g., healthcare facilities, experience of staff) characteristics can influence outcomes and risk of mortality.

Both type 1 and 2 diabetes are associated with chronic, progressive damage of the nerves, eyes, kidneys, and/or vasculature [13–15]. Target organ damage of this nature can be life-threatening and/or seriously disabling [16]. In a large proportion of persons with diabetes, other cardio-metabolic

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risk factors (hypertension, dyslipidemia, proinflammatory, and procoagulant states) often co-occur [17] which increases the risk of end-organ damage [18]. The frequency of these end-organ diseases varies according to the underlying phenotype, pathophysiology, as well as care and control of glycemia and other cardio-metabolic risk factors (i.e., blood pressure, cholesterol, and tobacco use) [19].

In this chapter, we provide an overview and update of diabetes management in the United States from a national perspective and examine several aspects of diabetes care including detection, health maintenance, and achievement of cardio-metabolic care goals. We further describe where and how diabetes has been managed over the past few decades in the United States and examine previous and ongoing disparities. We examine and report what local care delivery, payer, and policy interventions have been evaluated to improve quality of care and their respective impacts.

National Trends

Screening

As the national prevalence and absolute numbers of people with diabetes have grown, the proportion with undiagnosed disease has not changed dramatically [1, 20]. This has implications for disease burden as undiagnosed people are less likely to have a usual care provider or seek care, further lowering their likelihood of being diagnosed, and the progression toward end-organ damage continues [21]. In some cases, recognition of underlying diabetes is only confirmed when diabetes complications are evident. Indeed, national data show that approximately 40% of adults with previously unrecognized diabetes have some form of chronic kidney disease [22].

Similarly, with regard to prevention of diabetes, it is estimated that only about 1 in 5 of the 80 million adults with prediabetes in the United States are aware that they are at high risk of imminently developing diabetes [23]. This awareness gap is likely a major barrier to engaging people at risk of diabetes in evidence-based lifestyle or pharmacotherapeutic interventions to prevent diabetes [24, 25].

There are well-accepted glucose tests to diagnose prediabetes and diabetes and evidence-based lifestyle and pharmaceutical interventions to prevent and manage diabetes. There is also consensus that universal screening—i.e., offering glucose tests to the whole population—is not cost-effective, but rather, targeted screening of individuals at high risk for diabetes is both appropriate and economically sound [26–28]. To promote appropriate testing, expert committees at the American Diabetes Association (ADA) and US Preventive Services Task Force (USPSTF) regularly review the evidence and set recommendations for healthcare providers regarding whom to test and when [29, 30].

The ADA recommends glucose testing adults age ≥45 years or at any age with a body mass index (BMI) ≥25 kg/m^2 and one other diabetes risk factor (people who are physically inactive, have a family history of diabetes, are of minority race/ethnicity who did not identify as non-Hispanic white, have history of gestational diabetes or delivering a macrosomic baby, hypertensive [blood pressure ≥140/90 mmHg or antihypertensive medication use], have dyslipidemia [HDL-cholesterol <35 mg/dL, triglycerides >250 mg/dL, or lipid-lowering medication use], polycystic ovarian syndrome, known prediabetes, or known myocardial infarction, coronary heart disease, or stroke) [29].

The USPSTF previously recommended glucose testing in individuals with blood pressure >135/80 mmHg or antihypertensive medication use [31]. In 2021, the USPSTF changed their guideline and now recommend glucose testing between age 35 and 70 years in those who are overweight or obese [30]. The USPSTF guidelines also note that clinicians should consider screening earlier in persons with one or more additional risk factors (i.e., family history of diabetes, history of gestational diabetes, members of certain racial/ethnic groups such as African Americans, American Indians or Alaskan Natives, Asian Americans, Hispanics or Latinos, or Native Hawaiians or Pacific Islanders) since they may be at increased risk for diabetes at a younger age or at a lower body mass index.

In terms of the extent to which screening guidelines achieve their intended purpose, a study using national survey data showed that, during the period 2007–2012, only half of all US adults that would be eligible for glucose testing based on either the ADA or the older USPSTF criteria were actually offered a glucose test [32]. There is also a sizeable proportion of people (approximately 15%) that receive glucose tests despite not meeting sufficient criteria. Furthermore, in terms of guideline performance, findings suggest that the ADA and USPSTF guidelines are very different in their ideological focus: the ADA guidelines require a lower threshold for glucose testing with the aim of higher sensitivity, while the USPSTF recommendations are more focused on specificity. Despite this difference, the positive predictive value (or yield of people with dysglycemia of those eligible for screening) associated with each guideline was broadly similar—approximately 54–58% for identifying prediabetes or diabetes and around 5–7% for identifying undiagnosed diabetes.

More recent analyses examining the performance of the newer USPSTF guideline show that only 25% of patients would be eligible for screening. Though the newer guideline is more sensitive (~45%) and less specific (~72%), racial/ethnic minorities are less likely to be eligible for screening, perhaps due to their higher risk of diabetes at lower weight levels [33].

Management of Cardio-Metabolic Risks

It is encouraging that people with diagnosed diabetes do seek care. Nationally, 95% adults with diagnosed diabetes report having a healthcare provider and almost 92% report visiting the care provider twice or more in the past year [21].

Furthermore, over the past four decades, the scientific community has made important advances in clinical research. Large robust randomized controlled trials have shown that comprehensive management of cardio-metabolic risk factors, including glucose, blood pressure, and lipids, and avoiding tobacco, can delay both micro- and macrovascular diabetes complications [34–39]. It is on the basis of these trials and meta-analyses that diabetes management guidelines are set and revised by professional agencies (e.g., the ADA and the American Association of Clinical Endocrinologists [AACE]). These same guidelines are used to benchmark quality of care at local and national levels.

Using clinical care goals as targets, national survey data have been used to develop cross-sectional snapshots of how average adult Americans with diabetes are managing their cardio-metabolic risks. The data from consecutive national reports from the 1999–2002 to 2015–2018 surveys show that the proportion of adults with diabetes achieving glycated hemoglobin (HbA1c) levels <7.0% grew from 44.0% to 50.5%. The proportion of adults with diagnosed diabetes with BP <140/90 mmHg grew 64.0–70.4%, while the proportion meeting non-HDL-cholesterol <130 mg/dL increased dramatically from 25.3% to 55.7%; however, the proportions have leveled off since 2007. Though the proportion of adults with very poorly controlled glycemia (A1c <9.0%), blood pressure (BP >160/100 mmHg), and/or cholesterol (LDL >160 mg/dL), all declined. Of note, however, the proportions achieving control of all three risk factors have remained low, at 22.2% for 2015–2018, with little improvement since 2007 (Fig. 19.1) [40].

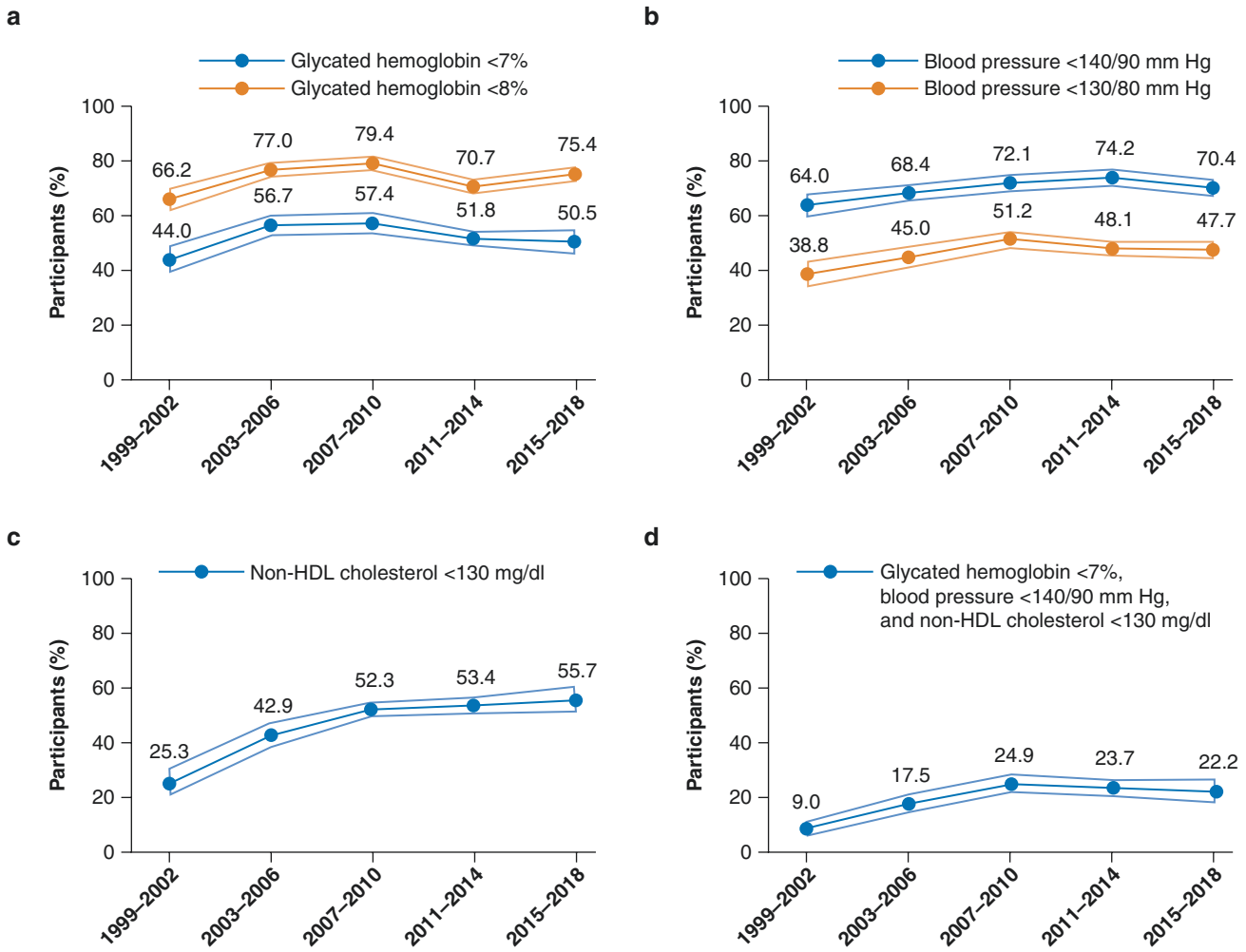


Fig. 19.1 Prevalence of glycemic, blood pressure, and lipid control among adult NHANES participants with diagnosed diabetes, 1999–2002 to 2015–2018. (**a**) Glycemic control, (**b**) blood-pressure control, (**c**) lipid control and (**d**) all risk factors controlled. (From Fang M, Wang D, Coresh J, Selvin E. Trends in Diabetes Treatment and Control in U.S. Adults, 1999–2018. N Engl J Med. 2021 Jun 10;384(23):2219–2228. Copyright © (2021) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society)

Table 19.1 Evolution of guidelines and care targets

	2010		2016		2021	
	Risk group	2010 target	Risk group	2016 targets[a]	Risk group	2021 targets
HbA1c (%)	All	<7.0	<45 y low risk	<6.5	All	<7.0[b]
			45–64 y low risk	<7.0		
			45–64 y med risk	<7.5		
			≥65 y low risk	<7.5		
			≥65 y med risk	<8.0		
BP (mmHg)	All	<130/80	All	<140/80	No CVD	<140/90
					CVD	<130/80
LDL (mg/dL)	No CVD	<100	40–75 y + DM	Statin	<40 y + DM + CVD risk factors; or >40 + DM	MI statin
	CVD	<70	High CVD risk	HI statin	CVD	HI statin

CVD cardiovascular disease, *y* years, *HI* high intensity, *MI* medium intensity

[a]Suggested targets by several authors; no formal guideline has endorsed specific targets other than generally supporting individualized glycemic goals [44, 45]

[b]More or less stringent glycemic goals may be appropriate for individual patients

National- and state-level efforts that drew greater attention to diabetes through measurement and action may have influenced trends in diabetes care. Movements like the National Committee for Quality Assurance (NCQA) and National Quality Forum have made major impacts through setting quality metrics, encouraging accreditation, and establishing performance measurement for healthcare systems. In turn, these processes may have facilitated [41, 42] better achievement of diabetes care goals. Similarly, individual states have used performance measures effectively—in Minnesota; for example, the Community Measurement initiative has reported on healthcare quality annually for a decade and can demonstrate performance for each of 1247 clinics or provider groups [43], and the state's average for meeting diabetes and cardio-metabolic care goals (38%) is higher than the national average (14%). These same successes are unlikely to be ubiquitous across all states, but no formal state-level analyses have examined this.

Other factors that may have contributed to these gains either positively or negatively include newer medications, provider education, changes in physician practice norms, the use of information technology, and electronic health record data, such as clinician decision support and the use of diabetes registries to track management of diabetes and performance measures and to couple audits with feedback. Payers for healthcare and hospital systems have also tracked and offered financial incentives (and disincentives) for care goal achievement (or lack thereof). On the patient side, there have been sustained efforts to educate patients and promote self-management. Each of these quality improvement efforts is discussed in greater detail later in the chapter.

There are limitations to using guideline treatment targets as performance metrics for health systems, localities, and the country at large. Although they are evidence-based, recommended treatment targets are not always what patients desire, and there can sometimes be a tension between quality of care from the health system and provider perspective and patient desires and satisfaction. Treatment targets are subject to change as new evidence is generated (Table 19.1), and these "moving targets" make it hard to understand whether there is any consistency in the patterns being observed. Furthermore, targets are usually dichotomous and can only convey part of the picture—for example, the mean levels of cardio-metabolic indices may be clustered around the target, but because of the single dichotomous metric, they get counted as "good" or "bad." Indeed, patients may also fare worse on specific aspects of their care, but better on others. As such, more "global" measures of disease risk (e.g., Framingham risk score, hospitalizations, quality of life, patient satisfaction, hypoglycemias) may provide alternative indicators than single dichotomous treatment targets.

Screening for Diabetes Complications

Aside from managing glycemia and cardio-metabolic risk factors to prevent diabetes complications, care guidelines [46–48] also recommend regular screenings to detect and treat diabetes complications. Earlier detection is aimed at identifying risk before irreversible target organ damage is incurred. All the microvascular complications of diabetes have a preclinical latent phase and well-accepted, sensitive, and specific eye, foot, and urine checks.

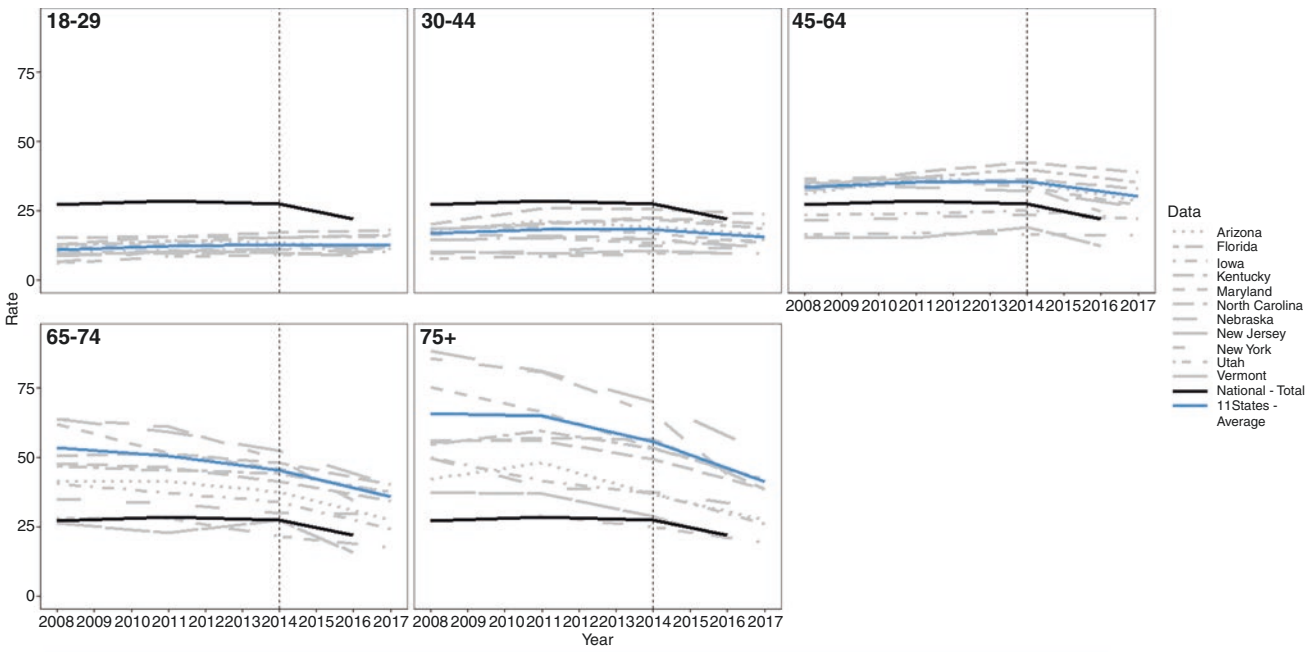
Diabetic retinopathy is very common and occurs in all people with diabetes, given sufficient duration of disease [49, 50]. Retinal screening [51] followed by photocoagulation therapy has been shown to significantly preserve vision [52, 53]. Neuropathy is also a common consequence of diabetes, and combined with compromised peripheral vascular circulation and poor wound healing [54, 55], ulceration [56], and infections [57, 58], can increase one's risk of gangrene and limb amputation. Regular foot checks and foot care are

considered invaluable to prevent foot ulceration and gangrene in people with diabetes [59, 60]. Regarding deterioration of kidney function, annual urine screening and the use of ACEi/ARB medications once micro-albuminuria sets in are both recommended [60]. Lastly, to lower infections, people with diabetes benefit from annual influenza vaccination and a lifetime pneumococcal vaccination [29, 61–65]. Repeated snapshots of national survey data between 2003 and 2018 show a plateau in the proportions of adults with diagnosed diabetes receiving all of these preventive screenings [20].

Incidence of Complications

The limitations of performance metrics notwithstanding the average 10-year cardiovascular event risk among Americans with diagnosed diabetes has declined over the past three decades, from 16.5% to 11.3% [66]. In keeping with this, between 1990 and 2010, nationally, there were substantial reductions in incidence rates of diabetes complications [67] and increases in life expectancy among people with diabetes [68]. There were marked decreases noted in incidence rates of acute myocardial infarctions (~68% decline), strokes (~53% decline), lower extremity amputations (~51% decline), and hyperglycemic death (~64% decline). The incidence of end-stage renal disease declined more gradually (~28% decline). However, more recent data suggests a reversal of this trend, with increasing hospitalizations for hyperglycemia from 2009 to 2015, and an increase in diabetes-related lower extremity amputations [69, 70]. Although visual impairment due to cataracts and retinopathy remain an important complication of diabetes, there are no reliable national estimates of trend patterns for these complications to date.

Another recent analysis of national and state-specific inpatient utilization data demonstrated a decline in diabetes-specific hospitalization rates by about 20% from 28.6 hospitalizations per 10,000 adults (n = 683,968) in 2011 to 22.0 hospitalizations per 10,000 adults (n = 537,394) in 2016/2017. This varied by age—older adults (65–74, 75+) had the greatest decrease in diabetes-specific hospitalizations (37.0–43.1% decrease), while we observed an increase in hospitalizations among the youngest age group (18–29) (18.5% increase, 95% CI 11.7, 25.3). See Fig. 19.2.



Hospitalization rates were calculated using numerator data from the HCUP Nationwide Inpatient Sample and State Inpatient Databases and denominator data from the IPUMS USA American Community Survey from years 2008-2017.

Two benchmark lines are highlighted: the black National-Total line shows national hospitalization rates across all US adults of all age groups and the blue 11 States-Average line shows average hospitalization rates across all states by age group.

The dotted vertical line delineates the point within our data that the data transitioned from rates generated using ICD-9 codes to ICD-10 codes. Rates post-transition may not be directly comparable to rates prior to the transition.

Fig. 19.2 Rates of diabetes-specific hospitalizations among US adults by age group; years 2008–2017. (Unpublished work from Turbow, S; et al. Trends and Sociodemographic Disparities in Diabetes Hospital Admissions: Analyses of Serial Cross-Sectional National and State Data, 2008–2017)

Gaps in Care

There are a number of ongoing concerning trends related to diabetes nationally. The absolute number of people with diabetes has grown substantially, approximately threefold over the past three decades [6, 71]. Large numbers of people still do not meet their care goals; the absolute numbers affected by disabling complications have increased; costs of care double every decade; and though excess mortality associated with diabetes has declined, there has been an expansion in the number of years people with diabetes live with disabilities [72]. Many of these concerns are at least partly attributable to gaps in access, suboptimal organization and delivery of healthcare and preventive services, and workforce shortages. We further examine these and other barriers and provide data from program and policy intervention studies as possible future directions for diabetes management to progress toward.

Outpatient Settings in the United States

Over the last 30 years, there has been a shift from hospital-based diabetes management to outpatient primary care. While earlier studies showed that hospital-based care provided better outcomes, health systems began shifting away from hospital-based diabetes management, and several studies showed that diabetes management in primary care setting was as good as hospital-based care and provided greater adherence to guideline-based preventive services [73–75]. Almost all of diabetes management is now in the ambulatory setting by primary care providers, and only 20% of patients with diabetes may be referred to an endocrinologist [76, 77].

Though fewer patients are managed in hospital-based settings for diabetes, admission rates for diabetes-associated complications (such as amputations, cardiovascular disease, and blindness) are still higher in the United States than in comparable countries [78]. Despite the availability and evidence of effective clinical guidelines, wide variation of the treatment of patients with diabetes remains in primary care [79]. Moreover, care gaps remain for many patients with diabetes [80].

Several challenges exist to achieving optimal diabetes care in the outpatient setting, which can be divided in three main areas: the patient, the provider, and the system.

The Patient

Patients must be able to access care, adhere to treatment, afford the care, and have the knowledge and skills to manage their condition on a daily basis. Access to care can often be determined by socioeconomic status and insurance status. Several studies have demonstrated that lower SES is associated with less access to specialist care, to diabetic preventive services, and worse control of diabetes [81–83]. Patients with private or public insurance are most likely to have met quality of care measures than those with no insurance [84]. A study using national data over the 1998–2008 period found that an estimated 16% of known patients with diabetes were uninsured and tended to have worse outcomes [85, 86].

Physical access to care continues to be a barrier. Lack of transportation, location in rural areas, and availability of healthcare personnel all play a role in a patient's ability to access care. Rural residents have higher rates of diabetes than urban residents and significantly greater barriers accessing reliable transportation. Moreover, rural residents can often spend more time trying to access care, thus creating higher cost from missed wages and time spent away from families to have improved quality of care [87]. Data from NHANES, 1999–2018, suggests that while there are no differences in diabetes care goal achievement in rural versus urban areas, adults with diabetes in rural areas were more likely to have multiple comorbid chronic health conditions [88].

Treatment adherence continues to be a major challenge in achieving adequate glycemic control. In one study of over 160,000 patients in Northern California, over 20% of patients with uncontrolled diabetes had poor medication adherence [89]. While the cause of this can be multifactorial, several challenges exist from the patient's perspective. First, lack of diabetes education can lead to poor understanding of the disease process and empowerment of the patient to play an active role in their care process [90]. While evidence supports the efficacy of diabetes self-management education in improving glycemic control, access is still limited [91]. Complex medication regimens and side effects from medications can also lead to poor adherence. Simplifying medication regimens can help address patient barriers to medication adherence [92]. The ADA Standards of Care guidelines recommend that providers address medication factors when reviewing treatment plans with patients to insure that they are simple, affordable, and manageable for the patient [29].

The Provider

Several provider level factors can influence diabetes care. Assessment of adherence can often be overestimated or missed by providers [92]. Patients are often asked to self-report their medication use without any objective assessment of actual medication adherence. In addition, providers are often reluctant to intensify therapy, though it may be clinically indicated; this is known as clinical inertia. Clinical inertia appears to be particularly common with regard to initiating insulin therapy and may also come into play with recent updated guidelines and initiation of novel antihyper-

glycemic medications (discussed below in "Diabetes Medical Management Updates" section) [93, 94].

Though clinical inertia is multifactorial and can be due to system and patient-level factors, one key area is patient-provider communication. Studies have shown that the quality of provider communication and patient's trust of their providers was associated with better outcomes. Better communication was associated with fewer misconceptions about insulin; thus, patients were more likely to begin insulin therapy, and this was associated with improved outcomes [95]. Several studies have also shown that providers who recommend individualized barrier assessment and tailored communication to patients can improve care [96].

The System

Several system-level factors create challenges to optimal diabetes care. First, dissemination of evidence-based practices can be slow. While evidence exists for optimal diabetes care, including processes of care, implementation of these evidence-based guidelines can vary. This can greatly improve through the use of guidelines to drive care, structured care management, and performance feedback [95].

Second, coordination of care can greatly improve outcomes. Evidence shows that optimal diabetes management in the outpatient setting requires a coordinated, systematic team-based approach. This strategy can help address several of the processes that create barriers to diabetes management. This is supported by team-based approaches where there are focus planned visits, education, and appropriate specialty care. Several models have been effective at demonstrating improved care coordination; these are discussed in detail later in this chapter. Many of these system level factors rely on accurate clinical data; this can also be improved by implementing electronic health records to track diabetes care outcomes and processes of care [95, 97].

Next, addressing financial barriers to patients for medications, health services, and education can greatly improve adherence and outcomes. Studies have consistently found that shifting costs to patients negatively affect outcomes in diabetes care. Increased cost to the patient resulted in lower medication adherence and lower rates of preventive care [98]. Those patients with full cost coverage were more likely to have appropriate diabetes-related care (such as dilated retinal exams), attended diabetes education, and practiced blood glucose monitoring.

Disparities in Diabetes Prevention and Management

Despite considerable evidence for preventing diabetes complications [34–39] and important advances in clinical care, there remain significant gaps in translating this evidence into policy and practice, specifically for vulnerable subpopulations (e.g., some age, race/ethnicity groups, and those with associated comorbid conditions) [21, 68]. Additionally, burdens of diabetes are not uniformly distributed across the United States; the Southeastern United States, for example, is disproportionately affected by diabetes and its complications [6, 99, 100].

Demographic Disparities

With reference to vulnerable populations, African-Americans, Hispanics, Native-Americans, and Asians/Pacific islanders all have higher rates of diabetes prevalence as compared to non-Hispanic Whites. The prevalence of diabetes among African-Americans is around 12.5% and for Hispanics is around 13%, compared to around 10% for non-Hispanic whites [20, 101]. These disadvantaged groups are less likely to receive diabetes-related preventive services, less likely to have access to care [21], and have lower health literacy. This lack of care leads to delayed diagnosis, advanced disease, and poor outcomes among these groups [102]. As the US population continues to become more diverse and the number of people with diabetes increases, addressing disparities in care will be increasingly vital.

While some studies have found no significant difference in most of the processes of care (including periodic hemoglobin A1c, lipid, microalbuminuria testing), those of racial/ethnic minorities and low-income groups tend to have poorer glycemic control [4, 103]. Furthermore, African-Americans and Hispanics have higher rates of diabetes-related complications resulting in hospitalizations, end-stage renal disease related to diabetes, and amputation [95, 104, 105].

Disparities also exist in care based on age. Younger adults with diabetes are less likely to receive periodic testing and more likely to have lapses in recommended care [21, 77]. Younger adults are less likely than older Americans to receive treatment when diabetes care goals are not achieved for glycemic and blood pressure control [40].

Socioeconomic Disparities

Socioeconomic factors contribute greatly to disparities in diabetes. Poverty, low education, and adverse neighborhood characteristics are often interrelated and continue to be concentrated in minority race/ethnic groups [106].

While numerous factors contribute to disparities in diabetes care, there are several potentially modifiable factors. One major contributing factor to poor diabetes outcomes is low health literacy and numeracy among minorities and patients of lower socioeconomic status. Defined as "the degree to which individuals have the capacity to obtain, process, and understand basic information and services needed to make appropriate decisions regarding their health," low health literacy can lead to low self-efficacy and disease knowledge and ultimate low diabetes self-management skills [107, 108].

Inherent to diabetes management is the ability of the patient to comprehend and apply diet and lifestyle instructions, measure and dispense medications, and quantify aspects of their care. Thus low literacy, which is often not assessed, can have major implications for patients' self-efficacy in diabetes management [108].

As mentioned above, access, especially insurance coverage, can greatly affect disparities in care. For example, a national study found that after controlling for demographic and health status characteristics, insurance coverage was more likely to determine whether a patient received diabetes services rather than race/ethnicity or socioeconomic status. It has been argued that expansion of insurance coverage would have the biggest impact of improving the quality of diabetes care and reducing disparities [109]. Studies have highlighted the implications that health policy can have on addressing disparities [110].

Disparities in Care Delivery

Unconscious bias at the provider and health-system level can also contribute to health disparities. Studies have shown that within the same provider panel, white patients had better glycemic control than African-American patients, independent of other sociodemographic characteristics, provider performance, or the number of African-Americans on their panel [103]. That said, while a majority of providers endorsed that racial disparities exist in diabetes care, only a small percentage of providers acknowledged the presence of racial disparities in their own practice [111]. Thus, unconscious stereotypes may be influencing physician behavior and ultimately the quality of the care provided.

Since the Institute of Medicine's 2002 report, "Unequal treatment: Confronting racial and ethnic disparities in healthcare," the evidence is growing that provider-level and system-level interventions that streamline processes of care and improve cultural competency can improve disparities in care [102]. For example, continuing medical education programs and personal feedback has shown to significantly improve diabetes process measure achievement (e.g., foot exams). Furthermore, assessment of health literacy, provision of culturally competent care, and improved awareness of disparities in care have been shown to be effective strategies improving diabetes care [112]. However, diabetes care disparities persist; further research and work to develop targeted patient-, provider-, and systems-level approaches to mitigate disparities in care for vulnerable populations are still needed.

Diabetes Medical Management Updates

Medical Management of Diabetes

Currently in the United States, most diabetes management is in the ambulatory setting. Primary care providers see a majority of the patients with type 2 diabetes in the United States [113]. Given the growing shortage of endocrinologists in America, this trend will likely continue into the future [114]. Studies have shown that there is a gap in adherence to the American Diabetes Association (ADA) guidelines when you compare primary care to endocrinology, with endocrinologists being more likely to adhere to the ADA guidelines [115]. Given the ongoing updates to outpatient management guidelines for type 2 diabetes, it will be crucial to change this pattern going forward given evidence that unstructured care has been noted to have worse outcomes for patients with diabetes [73].

Most Recent Changes in Guidelines

The ADA Standards of Medical Care in Diabetes has most recently been updated to reflect the growing body of literature that centers on adjusting cardiovascular risk [116] and mitigating risk of microvascular complications [117] with highly individualized diabetes treatment regimens. This segmentation may help clinicians with regard to choosing between the wide array of medications to lower glycemia that are currently available. To support this process, professional guidelines for glucose-lowering medications in type 2 diabetes have shifted to include specific guidance based on whether or not patients have either coronary vascular disease, heart failure with reduced ejection fraction, or chronic kidney disease [118]. Below we will review in detail some of the landmark trials that have shaped this shift in our management approach.

SGLT2-Inhibitors

In general, SGLT2 inhibitors have been associated with reductions in major adverse coronary vascular disease events and reductions in progression to end-stage renal disease. Specific trials are discussed in detail below.

1. Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)—Empagliflozin reduced the risk of death

from cardiovascular causes (38% relative risk reduction (RRR)) and reduced risk of heart failure hospitalizations (35% RRR) in type 2 diabetes patients with established heart disease when compared to placebo [119].
2. Canagliflozin Cardiovascular Assessment Study (CANVAS)—Canagliflozin reduced the risk of major adverse cardiovascular events (~15% RRR; $P < 0.001$ for noninferiority; $P = 0.02$ for superiority) and was associated with renal benefits in patients with type 2 diabetes [120].
3. Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Trial—Canagliflozin reduced the risk of kidney failure and cardiovascular events in patients with type 2 diabetes and kidney disease (~30% RRR) [121].
4. Dapagliflozin Effect on Cardiovascular Events-Thrombosis in Myocardial Infarction 58 (DECLARE-TIMI 58)—Dapagliflozin reduced the rate of cardiovascular death or heart failure hospitalization in patients with type 2 diabetes with or at risk for atherosclerotic cardiovascular disease (RRR 17%) [122].

DPP-4 Inhibitor and GLP-1 Agonists

A systematic review and meta-analysis of cardiovascular outcome trials for GLP-1 agonists noted that treatment with this class of medications has cardiovascular benefits, reduced mortality, and improved renal outcomes [123]. DPP-4 inhibitors have not been shown to have the same effects as noted below.

1. Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)—Sitagliptin had no clinically significant impact on either cardiovascular or renal outcomes [11.4% of the sitagliptin group vs. 11.6% of the placebo group [RRR <2%] (p for noninferiority <0.001)] [124].
2. Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) Study—Saxagliptin did not significantly affect the rate of ischemic cardiac events (7.3% and 7.2% [RRR ~1%], respectively, $P = 0.99$ for superiority; $P < 0.001$ for noninferiority) [125].
3. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) Trial—Liraglutide lowered the rate of first occurrence of death from cardiovascular causes and the rate of nonfatal MI and stroke (12% RRR) in patients with type 2 diabetes [126].
4. The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6)—Semaglutide reduced the rate of cardiovascular death and nonfatal MI and stroke (26% RRR) in patients with type 2 diabetes with high cardiovascular risk [127].

There is recent positive data for the dual GLP-1 receptor agonists and glucose-dependent insulinotropic polypeptides (GIPs) tirzepatide [128] and for the newer long-acting GLP-1 agonist efpeglenatide [129]. We may soon see these medications integrated into routine diabetes care in the United States.

Advancements in Diabetes Technologies

Technologies have advanced significantly over the years to include a wide range of insulin pumps and continuous glucose monitors (CGMs) that can help our patients with both type 1 and type 2 diabetes better manage their diabetes. Clinical guidelines recommend that the use of these technologies be tailored to individual patient circumstances [130]. The future advancement of these technologies will likely include improved hybrid-closed loop algorithms that allow for insulin pumps and CGMs to work more efficiently and effectively to improve glycemic control. The use of these technologies may be limited by insurance coverage and patient affordability.

Challenges and Barriers to Medical Management

Access to and affordability of diabetes medications, particularly insulin, remains of significant concern in the United States. A study looking at nationally representative data found that the cost of insulin had tripled from 2002 to 2013 [131]. Even with only three insulin manufacturers serving the market in America (Eli Lilly, Novo Nordisk, and Sanofi), there is a significant lack of transparency about the insulin supply chain which contributes to the excessive cost of insulin for patients [132]. The total patient expenditure on non-insulin antihyperglycemic medications has historically been lower than the total expenditure on insulin, but this may change as new patented medications emerge in the future [131] (Fig. 19.3). Ultimately, the true patient-facing cost of other glucose-lowering medications is difficult to ascertain due to the variability of insurance coverage of these medications.

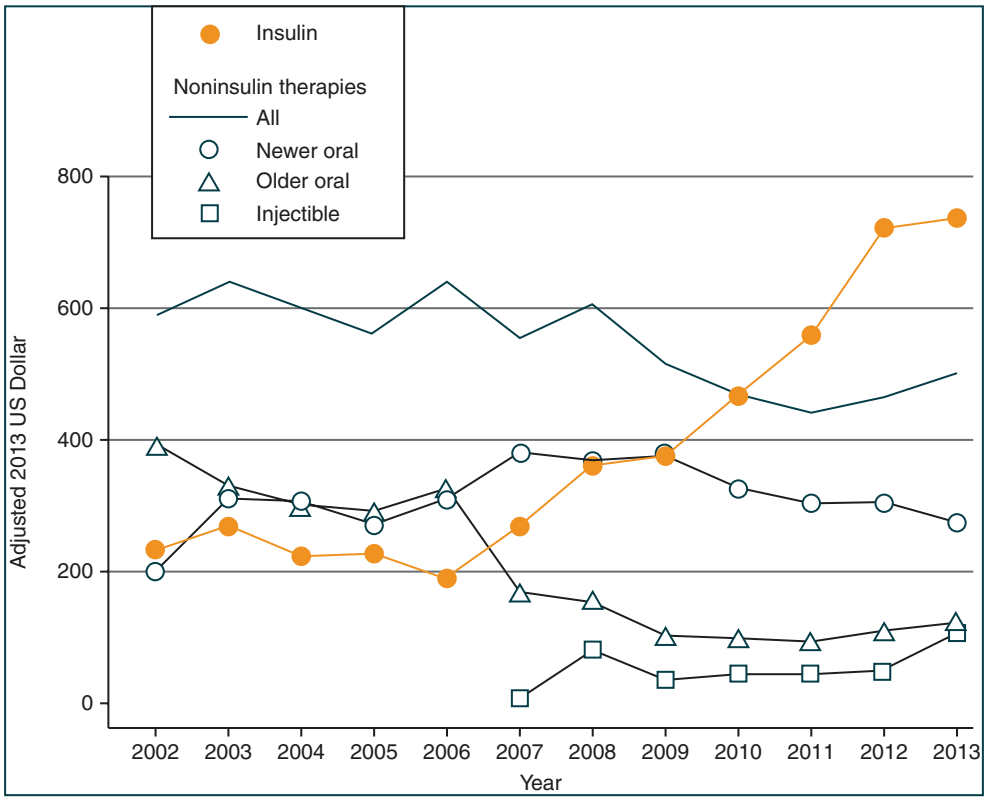


Fig. 19.3 Mean expenditure per patient for antihyperglycemic medications, 2002–2013. (From Hua X, Carvalho N, Tew M, Huang ES, Herman WH, Clarke P. Expenditures and Prices of Antihyperglycemic Medications in the United States: 2002–2013. JAMA. 2016;315(13):1400–1402. Reprinted with permission from the American Medical Association; License number: 5139441493361)

Quality Improvement Initiatives in Outpatient Diabetes Care

As mentioned above, there are barriers to achieving diabetes care goals at the patient- (e.g., low motivation), provider- (e.g., lack of therapy intensification), and/or system-level (e.g., fragmented care) [89, 133]. There are a number of patient-, provider-, and practice-level quality improvement (QI) interventions that have been devised to address these barriers [134, 135]. QI interventions include reminders, audits, and other tools to facilitate better self-management by patients and better care delivery by providers. The literature regarding QI interventions for diabetes management remains dominated by studies testing single interventions, usually focused on patients or providers, but not both. On aggregate, these interventions are associated with incrementally greater clinical benefits than routine care. A meta-analysis of 48 cluster and 94 individual randomized controlled trials [135] showed that, compared to usual care, QI interventions were associated with a 0.37 percentage point larger reductions in HbA1c; 3.1 and 1.6 mmHg larger reductions in systolic and diastolic blood pressures, respectively; and 3.9 mg/dL greater declines in LDL-cholesterol. On aggregate, even control arms experienced benefit, suggesting that more attentive follow-up alone may confer benefit in diabetes care.

Similar benefits were noted in a large pragmatic, cluster-randomized, parallel-group trial that assigned 343 European practices to screening and intensive treatment of multiple risk factors (i.e., small group educational meetings with family physicians and nurses to discuss treatment targets, algorithms, and lifestyle advice) versus usual care. Over 5 years of follow-up, the intervention clinic patients experienced greater improvements in cardiovascular risk factors (HbA1c, cholesterol, and blood pressure), but this was not associated with significant reductions in the incidence of cardiovascular events and deaths [136].

Though these single QI interventions are promising, diabetes patients usually face multiple interacting barriers, and sustaining risk factor control is challenging. As such, multicomponent QI interventions or "integrated" care models are recommended [137–143]. Integrated care attempts to address barriers by leveraging existing facilities, infrastructure, and human resources. Integrated clinical care models can be based in primary care or specialist care settings, and some examples of tested models include the chronic care model, collaborative care, and their more formal, contemporary patient-centered medical homes (PCMH) and accountable care organizations. The use of multicomponent QI interventions has shown some promise, even in randomized trials in low- and middle-income countries like India. One such trial enrolled patients with

mean HbA1c's of 9.9% and used nonphysician care coordinators to support patient self-management and decision-supported electronic health records to support treatment modifications by clinicians. This study showed sustained larger improvements in cardio-metabolic indices (0.5 percentage points larger HbA1c, 4/2 mmHg larger BP, and 7.9 mg/dL larger lipid reductions) than the control arm, as long as the intervention was continued (average of 30 months) [144].

Clinical Care Models and Practice Redesign

Conceptual Basis

Integrated clinical care models all embody similar principles. For example, collaborative care applies the principles of the chronic care model [137]. Collaborative care interventions have been shown to be of particular benefit in individuals with multi-morbidities like diabetes and depressive symptoms. Key components of the model include (1) focusing on defined patient populations and improving self-care among patients, (2) targeting depressive symptoms with medications and behavioral therapies, and (3) measurement-based treatment ("treating to target": regular review of patient population data, discussion of challenging cases, and recommending treatment modifications until clinical targets are achieved) [145].

A large number of randomized controlled trials have demonstrated that collaborative care is effective in the treatment of depression and anxiety in people with diabetes [146–151]. This has even been demonstrated in a randomized trial in India [152]. Collaborative care leads to greater adherence, larger reductions in depressive symptoms, more depression-free days, and better control of cardio-metabolic indicators [146, 151, 153–156]. However, there are two caveats. First, if the intervention is given for a defined period (e.g., 12 months in the INDEPENDENT study), there was no difference between the intervention and control groups in HbA1c at 24 months post-randomization, suggesting that persistent QI efforts are needed to sustain cardio-metabolic benefits. Second, there is a tension in collaborative care models as they have (sometimes conflicting) ideals: that of "treating-to-target" and of being "patient-centered." Very little is known about patient perspectives on these aspects of QI strategies in general—in a review of 554 qualitative research articles related to diabetes over 30 years [157], none used mixed methods to gather patient and provider perspectives on QI.

Regarding the value of multicomponent QI or integrate care models, cost-effectiveness studies have noted that upfront investments are offset by savings for future acute medical care [153, 158]. As such, collaborative care models do incur an upfront cost; it remains unclear whether US health delivery systems and payers view this as a worthy upfront investment [159, 160].

Application of Care Models for Diabetes

The chronic care model [137, 161] and collaborative care [162] concepts have inspired significant practice redesign to enhance diabetes care and outcomes over the past few decades [163]. A notable example has been the growing endorsement of medical homes [164]. Medical homes, also referred to as Patient-Centered Medical Homes (PCMHs) [165], were initially used in pediatric practices and later implemented more broadly after the American Academy of Family Physicians (AAFP) and the American College of Physicians (ACP) released position statements in 2004 and 2007 [166]. As mentioned above, the PCMH concept is based on the Chronic Care Model [167] and incorporates several core elements, such as team-based care, information technology, and payment reform, with the goal of providing more patient-centered approaches to the management of chronic health conditions (Table 19.2).

Within the Veterans Administration (VA) Healthcare System, medical homes are referred to as Patient Aligned Care Teams (PACTs) and have been used to help provide "patient-driven, proactive, personalized, team-based care focused on wellness and disease prevention resulting in improvements in Veteran satisfaction, improved healthcare outcomes, and costs" [170]. A typical VA PACT core team consists of a primary provider, a RN care manager, a clinical staff assistant, and an administrative staff member who work with a Veteran patient over time. The core team may also refer the patient to specialists as needed. Previous evaluations have shown that achievement of diabetes care goals in the VA system is as good or even better than in commercially insured programs [171].

In 2008, the NCQA developed a PCMH Recognition Program in collaboration with the AAP, ACP, AOA, and AAFP. An estimated 12,000 practices nationwide have now achieved recognition status [172]. On an annual basis, participating practices use an online platform to submit documentation on their performance in six categories, including (1) patient-centered access, (2) team-based care, (3) population health management, (4) care management, (5) care coordination and care transitions, and (6) performance measurement and quality improvement. The NCQA provides resources, such as training, education, and tools, to groups participating in the program [172].

Table 19.2 Features of PCMH and applications in diabetes care

PCMH feature	Description	Diabetes example
Team-based care with coordination and continuity	• Physician and nonphysician providers provide collaborative care	Physician refers patient on multiple medications to pharmacist for medication reconciliation and co-management
	• Team arranges care with subspecialists and consultants and guides the patient through the health system	
Information technology and quality tracking	• Incorporation of EHR → use of patient registries and clinical decision support based on updated practice guidelines, quality metrics	Use EHR data to identify patients with poor blood sugar control (i.e., HbA1C >9.0%) to provide targeted interventions (diabetes education, self-management, etc.) [168]
	• Checklists to ensure consistency	
	• Use of patient registries to review quality and performance data for entire system	
Enhanced access and comprehensive care	• Flexible scheduling system; easy access to the healthcare team	Clinic staff contact patient after complicated hospital stay to ensure patient has a follow-up visit within 7 days of hospital discharge
	• Comprehensive care including preventive care, education services, and end-of-life care	
Payment reform	• Quality-based payment and fee-for-service reimbursements	Payment incentives for meeting specified quality measures for diabetes care
	• Sharing of savings from reduced healthcare costs	

Adapted from references [164, 169]

Evidence

There is now an extensive and growing evidence base to support the PCMH model [173], especially for improving delivery of preventive services, patient satisfaction, and staff experiences, and reductions in emergency room visits [174]. A study of the Southeast Pennsylvania Multi-Payer Advanced Primary Care Practice Demonstration included 25 practices and showed improvements in lipid, blood pressure, and blood sugar control among patients receiving care for cardiovascular disease and diabetes [175]. A 2011 review of medical home demonstration projects also concluded that PCMH has been associated with improvements in quality and cost of diabetes care [164].

In more recent years, some medical home evaluations have shown less dramatic changes in quality and costs of care. For example, a 2014 study examined changes in the quality, utilization, and costs of care among 32 primary care practices in the Southeastern Pennsylvania Chronic Care Initiative between 2008 and 2011 [176]. Among 11 quality measures, significant differences were only observed in nephropathy screening in diabetes, and there were no significant changes in utilization or costs of care. However, the NCQA notes this study should be interpreted with caution since it was based on the NCQA's "earliest PCMH standards" with "only half of practices achieving the highest recognition level" [173]. In a recent observational study of primary care practices across Minnesota in 2020, building upon the experiences of demonstration practices, certified PCMH practices were more likely to meet composite diabetes care goals than uncertified practices (79.2% vs. 74.9%, $P = 0.01$) [177].

Lessons Learned

Demonstration projects have highlighted several important implementation challenges for medical homes [178]. These include (1) scheduling issues (i.e., time-limited visits and long wait times), (2) increased staffing needs, and (3) costly investments needed in EHRs [179]. It is worth noting that these challenges are often amplified for smaller practices, where resources may be more limited. A 2010 review also highlighted the "decline of the primary care workforce" (i.e., higher numbers of physicians, physician assistants, and nurse practitioners pursuing non-primary care specialties) and "lack of full patient engagement" (meaningful participation of patients in their own care) as other important challenges [163].

Policies and Incentives to Address Accountability and Quality in Diabetes Care

Polices and incentives focused on accountability and quality in diabetes care have increased significantly since the late 1990s. In particular, there has been an increased emphasis on the use of standardized performance measures, such as the Health Plan Employer Data and Information Set (HEDIS). HEDIS incorporates 81 measures across 5 domains of care and is used by most healthcare plans to measure performance of care and services [180]. The HEDIS diabetes measures originated from the Diabetes Quality Improvement Project (DQIP), which was a collaboration between the NCQA, the ADA, and Centers for Medicare and Medicaid Services (CMS) in 1997 [181]. The goal of the DQIP was to develop new QI measures for diabetes care and one of the first examples of the application of disease-specific measures on a national level. The DQIP measures included clinical measures of accountability (i.e., proportion with HbA1c testing

annually), quality improvement (i.e., self-management care), and patient survey data that are still used today in national assessments.

The HEDIS measures are now assessed annually including several diabetes-specific measures such as the percentage of patients receiving comprehensive diabetes care (i.e., annual HbA1c testing, glycemic control, retinal screening, LDL screening, etc.). Health plans are incentivized to use HEDIS measures since they are required to collect and submit this information in order to receive reimbursement. For example, the CMS requires health maintenance organizations (HMOs) to submit HEDIS data in order to get reimbursed for services provided to Medicare enrollees under the Medicare Advantage program [182, 183].

Pay-for-Performance Policies

Pay-for-performance programs, which also incentivize the use of quality measures, have been increasingly disseminated. The term pay-for-performance describes the use financial incentives to encourage health systems or providers to increase quality while decreasing costs (i.e., increase value) of health care and service delivery [184]. Quality measures may focus on processes, outcomes, structure, and/or patients' experiences with healthcare delivery. These incentives have been delivered in both the private (i.e., between a specific health plan and provider groups) and public (i.e., the CMS Value-Based Purchasing Program to provide incentives for providers) sectors. Financial penalties (i.e., no payment for service that does meet a specified quality metric) have also been included in some instances.

Studies evaluating the effects of pay-for-performance programs have shown mixed results [185, 186]. For example, a study of 1040 matched hospitals (n = 260 pay-for-performance hospitals and n = 780 control hospitals) found that while performance initially improved in pay-for-performance hospitals compared to control hospitals, there were no significant differences between groups at 5-year follow-up [187]. A recent review of 49 studies examining the effect of pay-for-performance on physicians, hospitals, and other settings also showed mixed results. Out of the 49 included studies, the only study rated as "good quality" did not find any significant improvements in diabetes outcomes (i.e., proportion with HbA1c and lipid control) [188]. Despite these mixed findings, there has been strong support for the use of pay-for-performance incentives as a means of aligning profits with improvements in patient care and "strengthen[ing] the business case for quality and safety" [189].

Several pay-for-performance programs, including accountable care organizations (ACOs) and Medicare's Hospital Re-admissions Reduction Program, were expanded under the Affordable Care Act (ACA). Some of the concerns regarding expansion of pay-for-performance programs include scope (i.e., will payments be large enough for providers to recoup their upfront costs in EHR/information technology to support data collection); unintended effects on the physician-patient visits and relationships (i.e., disruptions in clinical flow or forced disenrollment of noncompliant patients); and the potential impact on safety-net providers and existing race/ethnic and socioeconomic disparities (i.e., will providers avoid higher-risk patients which will further exacerbate of disparities in care) [190–193].

In addition to expanding pay-for-performance programs, the ACA also included several important provisions related to diabetes care [194]. A recent review highlighted several potential improvements in (1) diabetes screening rates, (2) access to diabetes care, and (3) structure of diabetes care resulting from ACA provisions [195]. The authors argue that up to 2.3 million out of 4.6 million adults with undiagnosed diabetes between 2009 and 2010 may have gained access to preventive care under the ACA as a result of provisions requiring health plans to provide free diabetes screening to those at risk and the establishment of the health insurance marketplaces, which makes health insurance more accessible. However, many states with higher prevalence rates of diabetes have not yet expanded Medicaid as of 2021, and more studies are needed to fully understand ACA impacts on diabetes care at the state and county levels.

COVID-19 and Telehealth

The COVID-19 pandemic required strict lockdowns and social distancing that prevented the routine care for adults living with diabetes. This led to the rapid adoption of telehealth, with support from all payers to provide these services [196], while the full impact of the pandemic on diabetes care is yet to be seen. Data suggests that patients with diabetes may have benefitted from telehealth services. In a survey conducted by the ADA, 73% of people with diabetes have used telehealth services during the pandemic, compared to just 11% prior to COVID-19. Of those who have utilized telehealth, 40% report that it has made it easier to manage their diabetes, compared with 37% who reported no change [197]. Thus, fueled by the pandemic, telehealth may be a potential care delivery platform for future diabetes care.

Research Gaps

Ultimately, success in addressing diabetes and related disparities will be contingent upon how rapidly, efficiently, and effectively existing evidence-based care programs can be translated, adopted, and sustained in clinical and community venues. More and rigorous theory-based translation/imple-

mentation research is needed. Implementation sciences involve studying the barriers and processes that lead to effectiveness of interventions (already proven in efficacy trials) in real-life clinical and community settings, as well as investigating the adaptations required to embed these interventions into routine practice. These data can help support communities, clinicians, and decision-makers to become increasingly skilled and comfortable with implementing programs and policies [198–200].

It must also be said that, to truly realize the "triple aim" of better health, better care, and lower cost for the nation with regard to diabetes [201], we cannot ignore the importance of prevention and the health policies needed to support this. The current growth in absolute numbers with diabetes, leveling off of achievement of diabetes care targets, and associated healthcare costs is untenable, and bending the cost curve requires greater adoption of interventions to prevent diabetes, whether they are targeted at the individual (e.g., intensive lifestyle interventions) or at the population (e.g., sugar-sweetened beverage taxes). However, more rigorous evaluation of population-based policies and interventions like taxation is needed. Studies assessing the long-term impacts of recent policy changes are also needed. The use of rigorous quasi-experiments has increased, and it is hoped that these shed light on appropriate and cost-effective policies and programs for employers, communities, counties, states, and even the federal government to adopt and invest in.

Concluding Remarks

The story of diabetes in the United States over the past 30–40 years is one of good and bad news. The evidence base for diabetes prevention and management has grown, and with that, there have been improvements in care and control of diabetes [80] and associated comorbidities. However, major gaps persist: (1) The proportion of people with undiagnosed diabetes and prediabetes has not improved; (2) engagement in prevention is exceedingly low; (3) rising costs of care and medications make achievement of targets out of reach for many Americans; and (4) young adults and disenfranchised populations with diabetes fare poorly in terms of control.

Furthermore, while incidence rates of "classical" diabetes complications like myocardial infarction, stroke, and amputations have dramatically declined in the last 20 years, the overall burden continues to rise due to growing numbers with diabetes and its complications, and there have been recent signals of increases in diabetes complications. Again, declines in incidence were less impressive for young adults, minorities, and low socioeconomic populations, and there have been increases in other diabetes complications like cognitive decline, depression, and heart failure. As such, it appears that younger people with diabetes will contend with classical complications earlier in life, and older Americans with diabetes will contend with more years of physical and mental disability. This has profound implications for US health care in terms of the volume, complexity (i.e., multimorbidity) of cases, and health system costs related to diabetes.

The changing demographics of people with diabetes in the United States has implications for care in terms of how those affected culturally and psychologically view their illness, if and how they access care, and progression of disease. Equally, the changing nature of how and where diabetes is managed will influence the impacts that this devastating disease places on this nation.

Multiple-Choice Questions

1. Which of the following statements is correct about trends in diabetes in the United States over the period 1999–2018?
   (a) Nearly 90% of people with diabetes remain undiagnosed.
   (b) The absolute numbers of people with diabetes complications like heart attacks and strokes has declined.
   (c) **The proportion of people with diagnosed diabetes achieving glycemic control has improved.**
   (d) All of the above are true.
2. Regarding quality of diabetes care in the United States, which of the following statements is false?
   (a) Since the 1990s, there have been concerted state, federal, and nongovernmental efforts to improve diabetes care goals through measurement and action.
   (b) **Treatment targets for diabetes are static and do not change as more and newer evidence is uncovered.**
   (c) Most of diabetes care is delivered in outpatient settings.
   (d) Comparing outpatient primary vs. specialty care for diabetes, studies have found no major difference in quality of care.
3. **True** or False: The United States experiences disparities in terms of diabetes-related health outcomes between people of different race/ethnicities, age, gender, and geographies.
4. Regarding the factors related to quality of diabetes care in the United States, which of the following statements is false:
   (a) **All gaps in quality are due to patient noncompliance.**
   (b) There are reports of unconscious biases that physicians have toward some of their patients which result in some patients doing better than others.

(c) Clinical inertia is a term to describe how physicians might be reluctant to prescribe certain therapies or intensify certain therapies—for example, insulin.
(d) System-level barriers to care like limited financial coverage for care have been associated with poorer health outcomes.

5. Which of the following statements best characterizes quality improvement interventions for diabetes?
   (a) Quality improvement interventions have no supporting evidence base and are mostly discovered by trial and error.
   (b) Quality improvement interventions mainly target patients since most of quality gaps are due to patient noncompliance.
   (c) **Gaps in diabetes care are usually multifactorial, and so interventions that address several barriers and are "integrated" are more likely to be effective.**
   (d) None of the above is correct.
6. Regarding delivering quality improvement interventions for diabetes, which of the following statements is most correct:
   (a) Quality improvement programs are only aimed at specialty care and have no place in primary care.
   (b) Each of the theories (e.g., the chronic care model, collaborative care, etc.) that underpin integrated care delivery is very different and does not have any common features.
   (c) The evidence to support quality improvement interventions for diabetes is weak (i.e., there are no randomized controlled trials or meta-analyses).
   (d) **None of the above is true.**
7. Patient-Centered Medical Homes (PCMHs) include which of the following features:
   (a) **Care coordination using physician and nonphysician providers**
   (b) Paper-based charting for most patient visits/encounters
   (c) Avoiding costly referrals to subspecialists and consultants
   (d) Enrolling healthier and younger subsets of patients to the practice
8. Regarding pay-for-performance programs, which of the following statements is false?
   (a) Pay-for-performance programs are used to incentivize the use of quality measures.
   (b) Pay-for-performance programs were expanded under the Affordable Care Act (ACA).
   (c) Pay-for-performance programs are used by both private and public insurance programs.
   (d) **Pay-for-performance programs have consistently led to improvements in patient care and outcomes.**
9. All of the following are associated with a lower likelihood of achieving diabetes care goals in the US except:
   (a) Black or Hispanic ethnicity
   (b) **Older age**
   (c) Younger age
   (d) Neighborhood characteristics
   (e) Low health literacy

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Diabetes Management in Africa

20

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Objectives

- To discuss the current issues related to diabetes management in Africa
- To review the most frequent treatment strategies and protocols for diabetes in Africa
- To discuss the challenges to the adequate management of diabetes in Africa

Introduction

Beside the fact that Africa is facing the most severe increase in the number of people with diabetes over time as compared with other regions of the world [1], Africans with diabetes face specificities that should be taken into consideration when approaching diabetes management in this area of the world. The most prominent specificities are (1) the absence of global healthcare insurance and coverage and the limited number and distribution of equipped healthcare facilities in most countries, both of which certainly account for the high frequency of acute and chronic complications; (2) the clinical heterogeneity marked by atypical phenotypes such as ketosis-prone type 2 diabetes [2].

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As a chronic disease, the management of diabetes in Africa as in other parts of the world has greatly evolved from the traditional protocols to a more holistic and patient-centered approach. However, the health systems in Africa are often ill-equipped to manage chronic diseases, because these countries still face significant mortality and morbidity from infectious diseases which take priority on most health policy agendas [3, 4]. Nevertheless, there has been significant progress in the types and coverage of diabetes care services.

It is, however, worth noting that despite the aforementioned specificities of diabetes, there are still limited contextualized guidelines, specific to the management of diabetes in Africa, as many countries still rely on guidelines essentially used in developed countries [5, 6]. The integration of diabetes care programs in the health system has been one of the innovative methods adopted by a number of countries in Africa to improve the management of diabetes. Alongside these programs, associations are being set up in several countries to coordinate actions at national level, all in a bid to control the burden of this disease [4].

Regarding the pharmacological means to treat diabetes, most oral antidiabetic agents are available in Africa, though the newest ones may not be financially accessible to most patients. While traditional formulations of human insulin are more accessible in most countries, insulin analogs in pens, though present in most markets, are still very expensive. Finally, attempts to define the role and include African traditional medicine and phytotherapy in the management strategy of diabetes seem to be of great interest, as these alternatives are often the recourse of many patients, because of their limited financial means and the chronic nature of the disease.

As in other parts of the world, the objectives of management of diabetes in Africa are centered on improving the quality of life of patients, reducing morbidity and mortality through prevention of disease progression, and development of complications [7]. Despite the lack of general guidelines for the management of diabetes in Africa as a whole due to the specificities of this chronic disease, some countries like South Africa, Tanzania, and Nigeria among others have produced context-specific national guidelines [8–10]. The

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importance of these guidelines cannot be overemphasized, given the fact that they provide a contextualized framework for rational management decisions and a guide for training healthcare providers on up-to-date evidence-based practices for diabetes management. Overall, these guidelines help to improve on the quality of care delivered to patients and reduce diabetes-related mortality and morbidity [8].

The management of diabetes in Africa can be approached from the following four perspectives:

1. Health beliefs and perceptions relating to diabetes
2. Management of blood glucose
3. Prevention and management of acute metabolic and chronic complications of diabetes
4. Management of comorbidities

Health Beliefs and Perceptions Relating to Diabetes in Africa

For a better approach to the management of diabetes in Africa, it is important to understand the beliefs, knowledge, and perceptions relating to diabetes and related risk factors. In this first section, we shall describe the health-seeking behaviors of people with diabetes in Africa and how this influences the prevention and control of diabetes.

Health-Seeking Behaviors of People with Diabetes in Africa

In Africa, although most patients believe that the ideal place to seek treatment for general health care including diabetes is a modern healthcare facility, patients often seek alternative or complementary treatment from folk healers and other sources, mainly because they lack money to pay health service bills. Money is seen as a major determinant of where, when, and which kind of treatment is sought during illness. Patients tend to use traditional therapies because of beliefs about the causes of their ill health and a strong cultural attachment to initial home management and only access modern health services during a crisis. Concerning some of the risk factors for diabetes, some people believe that obesity is a sign of good living and/or good health and that eating healthy is hard to sustain because of practical difficulties. Others consider less strenuous activities such as walking to be a sign of poverty and therefore see this as demeaning.

Figure 20.1 describes the behavioral factors and beliefs associated with the development and progression of diabetes in Africa. This highlights on the relative importance of various health beliefs toward a cultural understanding of diabetes in Africa.

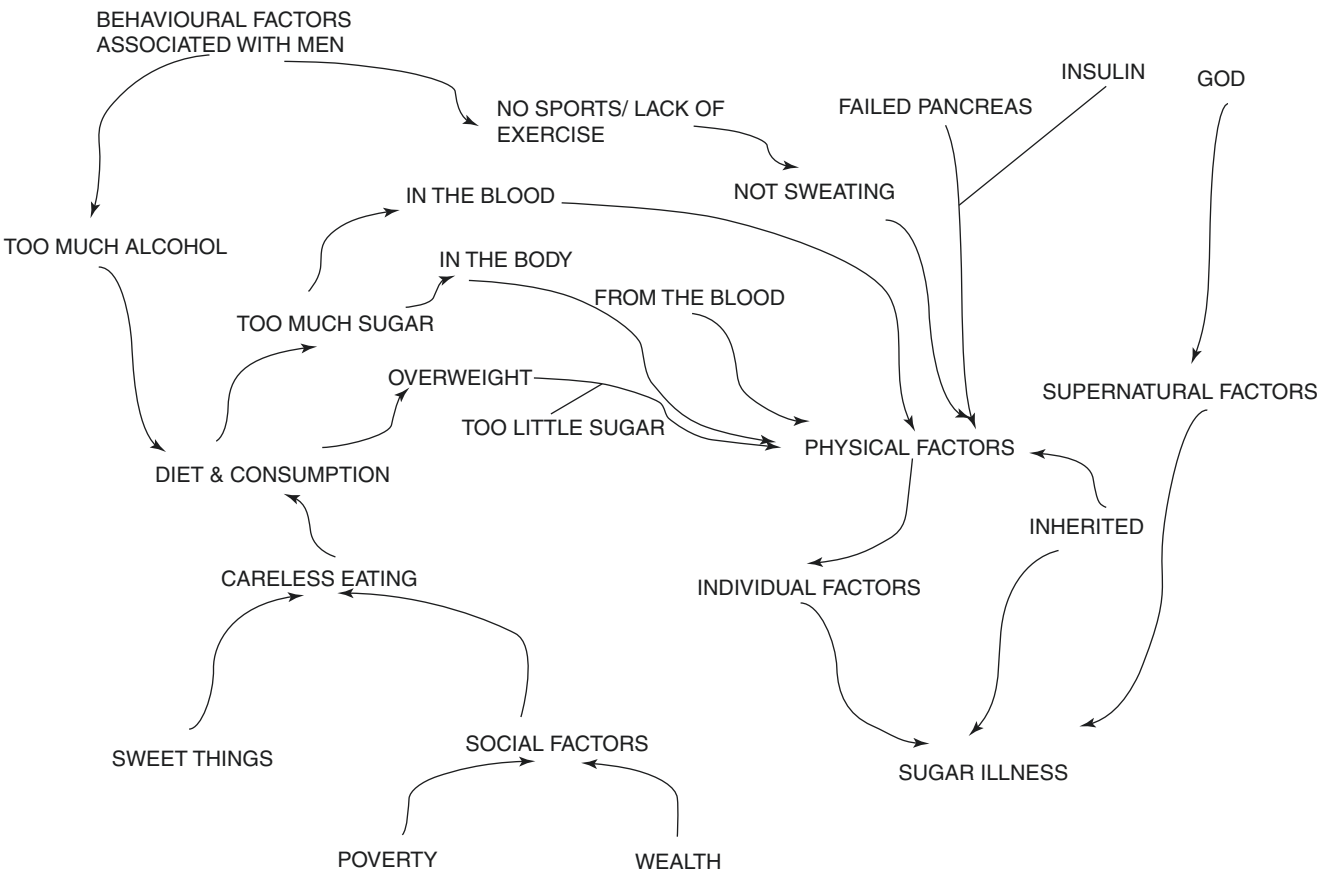

Fig. 20.1 Causal Web of Diabetes in Africa (Professor Jean Claude Mbanya, personal communications 2014)

Impact of These Beliefs on the Prevention and Control of Diabetes in Africa

Due to the beliefs described above, many people are not motivated to take action to reduce their risk of diabetes by increasing activity, changing their diet, and losing weight. In addition, home management for symptomatic relief is accepted as essential because patients taken to the hospital are thought to be likely to die. This lack of knowledge, lay beliefs about causation and treatment, and financial barrier, increase the likelihood of diabetes and its complications to be managed at home or consultation of traditional healers, thereby delaying presentation to health services. Since the diagnosis of diabetes is late in Africa, most patients already present with complications at the time of diagnosis.

Figure 20.2 illustrates the strong interplay between health beliefs, knowledge, lay perceptions, and health behavior of patients with diabetes in Africa and how this influences its prevention and control. This shows that health outcomes of patients with diabetes in Africa are highly dependent on knowledge and cultural beliefs.

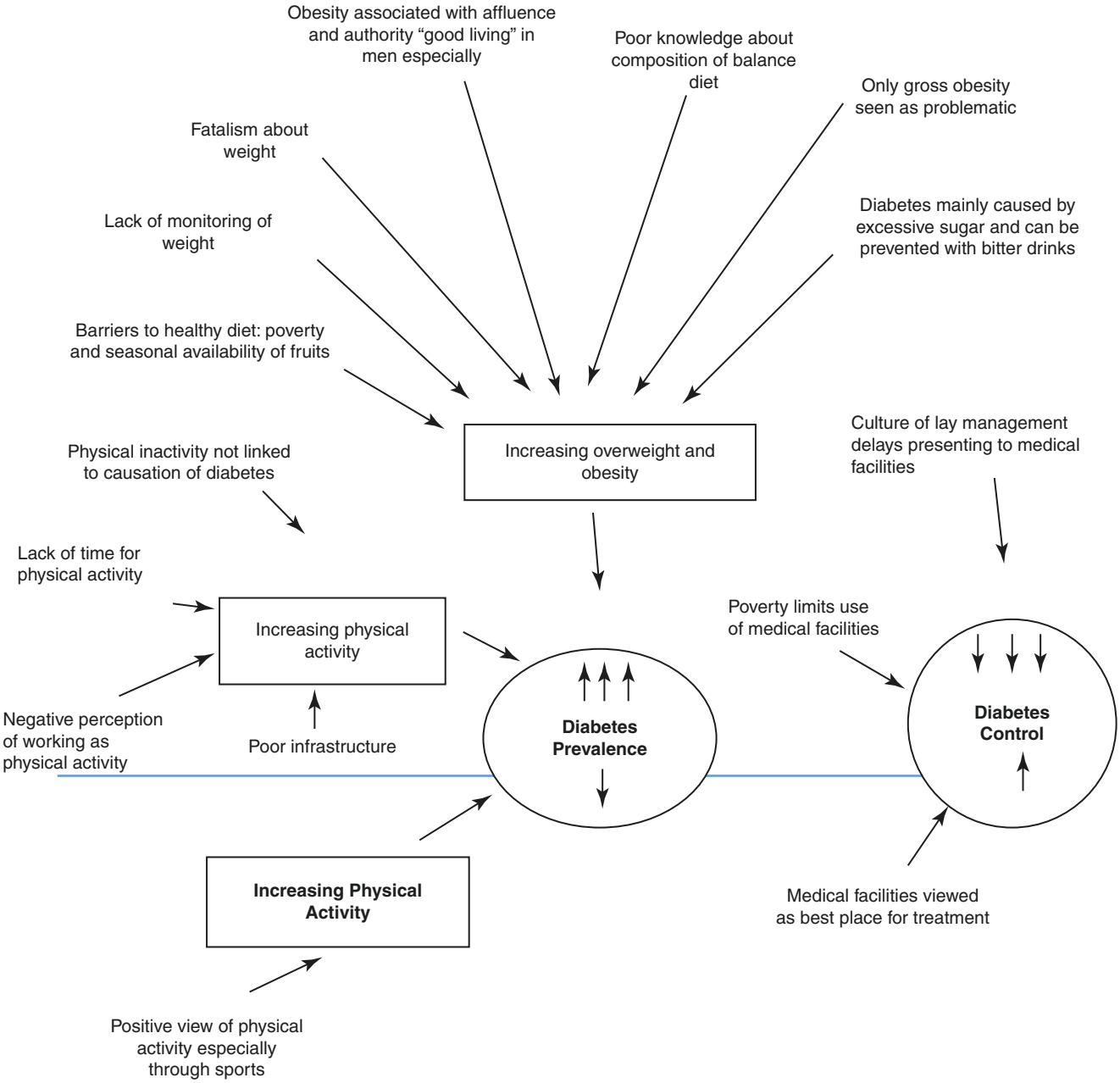

Fig. 20.2 Impact of lay health beliefs on the prevention and control of diabetes in Africa [11]

Management of Hyperglycemia

Maintenance of an optimal blood glucose level is fundamental to managing diabetes. This is because the complications of diabetes arise when the chronic hyperglycemia that characterizes diabetes mellitus remains untreated. Normal glycemic control can be achieved using non-pharmacologic and pharmacologic means. Non-pharmacologic means are the first line of treatment, and pharmacologic means are employed in combination. Medical nutrition therapy is the first line of treatment among the non-pharmacologic options [7]. It is worth noting that the therapeutic benefits of pharmacologic therapy are optimal when used alongside medical nutrition therapy.

Objectives of Management of Diabetes Mellitus

- Improve on the early detection of disease in affected individuals.
- Improve the quality of life of patients with diabetes.
- Prevent disease progression to complications.
- Empower patients and encourage self-care practices.

Screening and Diagnosis

The asymptomatic presentation of diabetes in its early stages compromises health-seeking behavior, even among susceptible individuals. It has been estimated that a quarter of patients with diabetes at the time they seek medical attention already have complications resulting from the disease [8]. Less than 50% of participants from most studies conducted in sub-Saharan Africa were known to have diabetes with reported within-country variations; the higher percentages reported in urban areas compared to rural areas [5]. Screening is important in the early detection of disease before the occurrence of complications, thereby reducing disease morbidity and mortality [8]. Even though the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION)-Cambridge study found that screening for type 2 diabetes is not associated with a reduction in mortality, the careful interpretation of these findings in a resource-limited context as sub-Saharan Africa has been strongly recommended to avoid drawing faulty conclusions and inferences [12]. This is because the socioeconomic context makes Africa the area where screening is most likely to be beneficial.

Nevertheless, the implementation of large-scale population-based screening in the African context is limited by the scarcity of both human and financial resources, since well-organized clinics with suitably trained staff in diabetes screening and care are necessary for an effective screening program. Targeted screening conducted at local healthcare facility level and focused on individuals with increased disease risk is therefore preferred. Logistically less-demanding screening methods, such as risk scoring systems and questionnaires with minimal or no laboratory testing required, have been proposed for identifying people at high risk of developing diabetes [13]. The screening of diabetes is often undertaken alongside other cardiovascular risk factors such as hypertension and hyperlipidemia to ensure a holistic approach to patient care. The Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines recommend screening for type 2 diabetes mellitus in all overweight adults at any age so long as they have another risk factor for diabetes, all other adults with no risk factors and aged 45 and above, with rescreening after 3 months to 3 years depending on individual risk [10]. The International Diabetes Federation, however, recommends screening for type 2 diabetes mellitus in individuals aged 40 and above, with familial predisposition, elevated body mass indices, and other cardiovascular risk factors such as high blood pressure and dyslipidemia [14].

Screening of Type 2 Diabetes Mellitus

For who?

- Age ≥ 45 if no risk factor
- Any age if overweight or obese with one other risk factor:
  - Family history of diabetes mellitus
  - Hypertension
  - Hyperlipidemia
  - Physical inactivity
  - Pregnancy/gestational diabetes

Methods

- Fasting blood glucose measurement
- 2 h blood glucose (oral glucose tolerance test)
- HBA1c

Review durations

- 3 yearly in case of negative screening test
- Yearly follow-up in case of positive screening test but negative diagnostic test results.

Adapted from the 2017 SEMDSA Guidelines for the Management of type 2 Diabetes [10]

The criteria for diagnosis of diabetes in Africa are similar to those recommended by the international guidelines [15]. Most patients present with acute hyperglycemia with undoubted clinical manifestations; others are diagnosed through campaigns screening or labor health screening. Oral glucose tolerance test is seldom performed, whereas using HbA1c as a means of diagnosis seems illusive because of the absence of the recommended method (high-pressure liquid chromatography) in most African countries.

Lifestyle Modification

The principal components of lifestyle modification in the African context just as in other parts of the world are diet control, weight control, physical activity, cessation of alcohol consumption, smoking, and other factors known to favor hyperglycemia or to increase the risk of complications.

Components of Lifestyle Modification
Healthy diet:

- Reducing carbohydrate, saturated fat, cholesterol, and salt intake

Weight reduction:

- Target BMI: 18.5–24.9 kg/m^2

Regular physical activity:

- Aerobic exercises (brisk walking, cycling, swimming, dancing, water aerobics)
- Resistance exercises (free-weight lifting, exercises with weight machines)
- At least three times/week and between 20 and 30 min per session
- Reconsider insulin and secretagogues dosing to prevent hypoglycemia
- Consider cardiovascular assessment before and contraindications to physical activity

Reduction of alcohol consumption
Cessation of smoking

Adapted from the 2012 and 2017 SEMDSA Guidelines for the Management of type 2 Diabetes [8, 10]

Medical Nutrition Therapy

The effects and benefits of medical nutrition therapy are two-pronged to maintain glycemia within normal limits and also to help reduce body weight which is a modifiable risk factor of diabetes. Adjustments of the diet revolve around a personalized diet based on an assessment of the patient's nutritional status within the context of sociocultural and psychological influences and tailored to the patient's needs based on ongoing monitoring of glycemia and patient support to maintenance of this plan with allowance for flexibility. Even though most patients with diabetes in Africa are aware of the importance of a healthy diet in its management, some are not aware of the specific components of the healthy diet [16].

In addition to this, lack of adherence even when the healthy diet is initiated remains common [10]. Regular medical nutrition therapy contact sessions with dietitians specialized in diabetes management are therefore recommended over the generic nutritional advices and messages often given to patients [10]. Restrictive diets consisting of protein-rich, carbohydrate-free, and fat-free items are not recommended due to no proven long-term benefit [8].

Specific dietary requirements in patients with type 2 diabetes mellitus are as follows:

1. Healthy diet:
   (a) Increasing daily water intake and having meals at regular times daily
   (b) Avoiding binge eating
   (c) Variety of vegetables and fruits excluding fruit juices
   (d) Low-fat dairy products, meat alternatives, and fish
   (e) Limiting processed food
2. Carbohydrate:
   (a) Constitute 45–60% of total energy intake
   (b) Monitoring carbohydrate intake and limiting sugar alcohols
   (c) Reasonable sucrose and fructose and artificial sweeteners intakes are acceptable
3. Fats:
   (a) Should be <35% of the total energy intake
   (b) Limiting saturated and poly-saturated fats intake
   (c) Consume monounsaturated fat and omega-3 fatty acids from both plant (flaxseed, walnuts, and canola) and marine (fatty fish) sources instead of saturated fat
4. Proteins:
   (a) Should make up 15–20% of total energy intake
5. Salt:
   (a) Reducing dietary salt intake to control blood pressure (<2300 mg/day)
6. Vitamins and minerals:
   (a) Routine supplementation not required unless in some specific groups such as elderly patients or lactating pregnant women

7. Alcohol:
   (a) Moderate alcohol consumption for individuals who consume alcohol (1 unit per day for women and 2 units per day for men)

These dietary requirements often difficult to accurately measure have been simplified in the healthy diabetes plate concept (Fig. 20.3a, b).

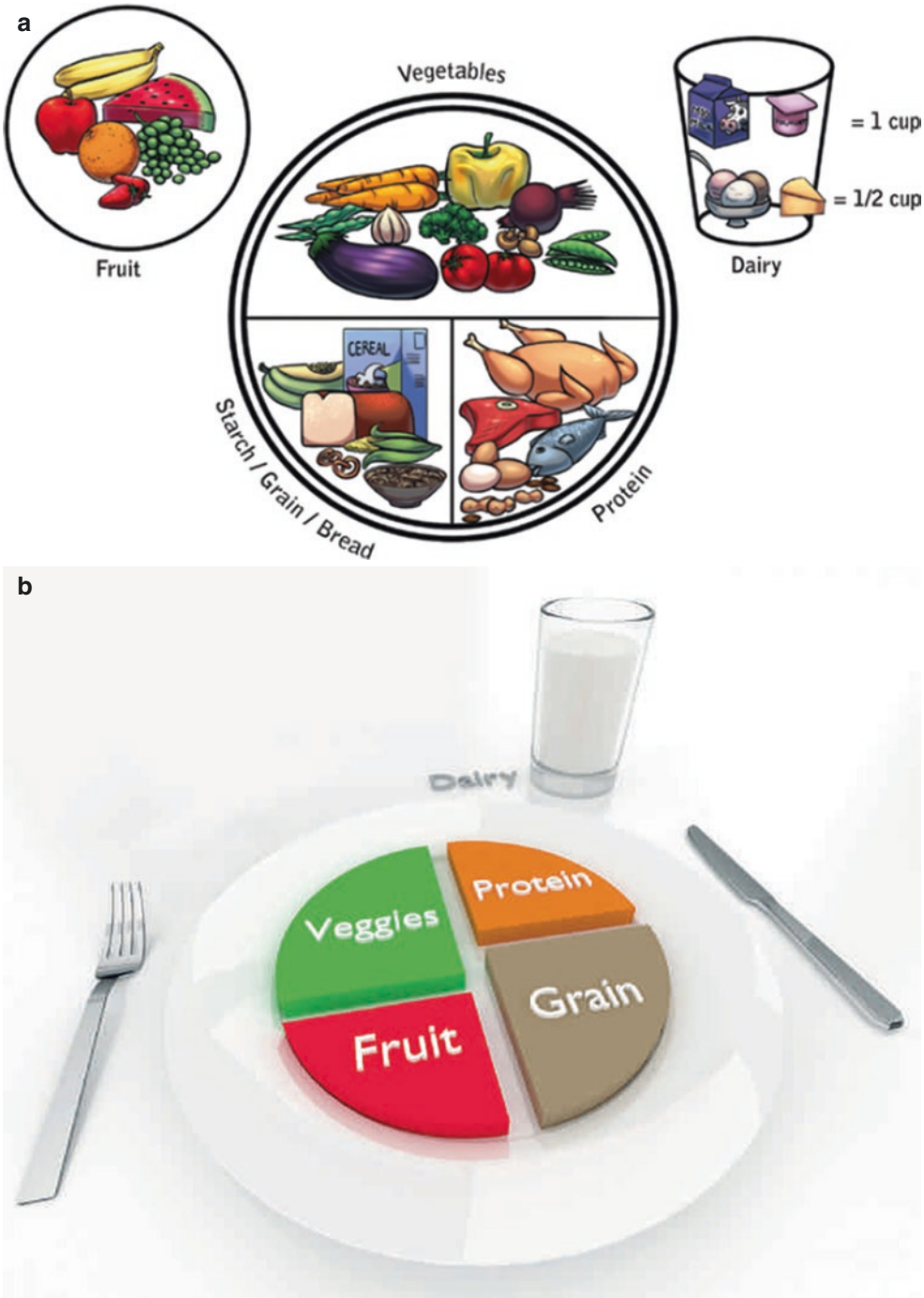

Fig. 20.3 (**a**) The healthy diabetes plate. (*Source: The 2012 SEMDSA Guideline for the Management of type 2 Diabetes* [8]). (**b**) The healthy diabetes plate (*Source: Management of Gestational Diabetes in the Community. Training manual for community health workers* [17])

The Healthy Diabetes Plate

To constitute the healthy diabetes plate:

- Divide into two equal halves, and then divide one of these halves into two equal sections.
- The undivided half section should consist of a variety of non-starchy vegetables, such as spinach, carrots, lettuce, and other greens, cabbage, green beans, broccoli, cauliflower, tomatoes, cucumber, beets, mushrooms, and peppers.
- One of the quarters should contain starchy foods, such as whole-grain breads (e.g., whole wheat or rye), whole-grain high-fiber cereal, cooked cereal (e.g., oatmeal), brown or long-grain rice, pasta, baby potatoes, green peas, sweet potatoes, whole-grain crackers, and fat-free popcorn.
- The other quarter section should contain meat and meat substitutes, such as skinless chicken and Turkey portions, fish and other seafood, lean cuts of beef and pork (e.g., sirloin, fillet or pork loin), tofu, soya, eggs, and low-fat cheese. Avoid processed meats (e.g., salami, Vienna sausages, and polony), which are high in fat and salt.
- A glass (240 mL) of nonfat or low-fat milk, or 180 mL of light yoghurt (at least 2 servings per day).
- A medium portion of fruit (such as oranges, apples, pears, or small bananas), or two small fruits (such as plums or peaches), or three quarters of a cup of fresh fruit salad. Instead of eating fruit with meals, these are eaten as snacks between meals.

Physical Activity and Other Lifestyle Measures

With obesity and overweight as risk factors for insulin resistance and type 2 diabetes mellitus, weight loss stands out as an important factor to be considered in order to prevent or manage diabetes mellitus. Adjustments in weight should therefore be tailored to match the individual's height to maintain a normal body mass index (18.5–24.9 kg/m^2). The place of patient education on weight loss and its importance in diabetes management cannot be overemphasized, since local perceptions in the African setting consider obesity as an indicator of affluence, status, and good living [11]. Significant reductions in diabetes mellitus-related mortality and morbidity have been reported with regular physical activity [18, 19]. As reported in the findings of a study on a cohort of diabetes mellitus patients in Cameroon, Central Africa, a 12-week aerobic exercise program monitored by a step counter was found to significantly improve the anthropometric and metabolic parameters, alongside the aerobic capacity of patients with diabetes mellitus [19]. The aerobic exercise here consisted of 45-min sessions holding thrice a week with each session consisting of a warm-up, brisk walking or light running, and a cooldown. Dancing was also introduced at some point during the follow-up period of the aerobic exercise [19]. Despite being aware of the importance of physical activity in preventing or managing diabetes, several patients in sub-Saharan Africa still do not engage into physical activity due to lack of time or access to appropriate infrastructure [11].

Overall, physical activity reduces cardiovascular disease risk; improves insulin sensitivity; controls glycemia, blood pressure, and lipid levels; and reduces the total body weight. It is worth noting that any recommendations to engage in a physical activity regimen should be preceded by an adequate assessment to ensure there are no contraindications to physical activity.

The multicenter Diabcare Africa conducted in six African countries study reported rather low rates of smoking and alcohol consumption among patients with diabetes mellitus in sub-Saharan Africa, with the highest figures detected in Central African regions [20]. Reduction in alcohol consumption to a maximum of 1 unit per day or less for women and 2 units per day for men is beneficial in preventing any alcohol-related hyperglycemia [8].

Pharmacologic Therapy

Pharmacologic therapy is considered in addition to lifestyle modifications or when the latter has failed to maintain optimal glycemic levels. In type 1 diabetes, and in any acute metabolic and non-metabolic diabetes presentation, insulin therapy is usually mandatory. As in other parts of the world, the two principal pharmacologic therapies used in Africa are oral antidiabetic medications and insulin therapy, used individually or in combination depending on the type of diabetes and patients' individual circumstances. Over the past decade however, non-insulin injectable antidiabetic drugs led by glucagon-like peptide-1 (GLP-1) have emerged as an essential part of diabetes management [21]. Many patients in

Africa, however, believe that diabetes can be treated using traditional therapy, making compliance to recommended pharmacologic therapy occasionally ineffective [11].

Treatment Targets

Blood Glucose

- Fasting plasma glucose (FPG): 4–7 mmol/L
- Two-hour postprandial plasma glucose (2-h PG) 4–8 mmol/L

Glycated Hemoglobin [10]

- Glycated hemoglobin A1c (HbA1c)c ≤ 7%
- HbA1c <6.5% in newly diagnosed patients in good health

Considerations [10]

Involve patient in discussion on glycemic targets

Three monthly HbA1c monitoring in patients not at target and six monthly if target achieved

Oral Antidiabetic Medications (OAD)/Oral Hypoglycemic Agents (OHA)

Majority of patients in Africa on pharmacologic therapy for diabetes are on oral antidiabetic medications [20], since they are generally the first line in type 2 diabetes treatment protocols. Monotherapy or combination therapy with different oral antidiabetic agents is used based on the potential factors underlying the hyperglycemia of the patient, and combination therapy should be based on agents from different classes. The multicenter Diabcare Africa study reported that more than half of patients on pharmacologic therapy were receiving two oral antidiabetic agents for treatment of their diabetes, and very few patients had up to three agents [20]. Nevertheless, treatment should be individualized, based on patient sociodemographic and clinical characteristics as well as economic status. The use of generic medications with proven efficacy is highly encouraged in the African context due to their relative affordability compared to proprietary brand [7]. The biguanide metformin and sulfonylureas agents are often used as first-line agents unless contraindicated. The most commonly used oral antidiabetic agents and their respective characteristics are summarized in Table 20.1.

Table 20.1 List of antidiabetic drugs available in Africa

Medication	Starting dose	Maximum dose	Adverse effects	Contraindications
Biguanides				
Metformin	500 mg	2550 mg	Abdominal pain	Renal failure
			Nausea	Hepatic failure
			Loose stool	Cardiorespiratory failure
			Lactic acidosis	Pregnancy
Sulfonylureas				
Glibenclamide	2.5 mg	20 mg	Hypoglycemia	Pregnancy
Gliclazide	40 mg	320 mg	Weight gain	Caution with hepatic and renal disease
Glimepiride	1 mg	8 mg	Skin rashes	
Glipizide	5 mg	40 mg		
Chlorpropamide	100 mg	500 mg		
Tolbutamide	500 mg	2500 mg		
Tolazamide	100 mg	1000 mg		
Acetohexamide	250 mg	1500 mg		
Thiazolidinediones[a]				
Rosiglitazone	4 mg	8 mg	Hepatic impairment	Renal failure
Pioglitazone	15 mg	45 mg	Fluid retention	Hepatic failure
			Weight gain	Cardiorespiratory failure
			Dilutional anemia	Pregnancy
Meglitinides				
Nateglinide	180 mg	360 mg	Hypoglycemia	Cardiac failure
Repaglinide	1.5 mg	16 mg	Weight gain	Hepatic failure
			Dyspepsia	Pregnancy
Alpha-glucosidase inhibitors				
Acarbose	25 mg	300 mg	Dyspepsia	None
Miglitol	25 mg	300 mg	Loose stool	

Source: Type 2 diabetes mellitus clinical practice guidelines for sub-Saharan Africa [7]

[a] This class is currently absent in most African countries because of the issues on the cardiovascular safety of rosiglitazone

Insulin Therapy

In general, insulin therapy is used in type 2 diabetes: when oral antidiabetic agents are inadequate to maintain optimal blood glucose levels; in cases of acute hyperglycemia requiring rapid correction; and in pregnancy where most oral antidiabetic agents are contraindicated. In type 1 diabetes, insulin is the compulsory treatment. Africa, however, faces the major problem of limited availability of insulin analogs and even unaffordability when available [5], and frequent run-out of human insulin formulation which are more accessible. Nevertheless, insulin therapy should begin as soon as indicated in the management of diabetes, whether in combination with oral antidiabetic agents or as monotherapy.

Insulin Therapy

Indications:

- Type 1 diabetes mellitus
- Poor glycemic control with OAD
- Contraindications of OAD
- Hyperglycemic emergency
- Severe glycemia at initial presentation
- Perioperative glycemic control
- Organ failure (cardiorespiratory, hepatic, renal)
- Pregnancy

Regimens:

Combination therapy:

- NPH (0.2 IU/kg of body weight/day – Administered at bedtime) +
- OAD (metformin and reduced or stopped sulfonylureas dose)

Monotherapy:

- Premixed insulin twice daily, given half an hour before morning and evening meals

(0.2 IU/kg of body weight/day)

OAD, *oral antidiabetic agents*; *NPH*, *Neutral Protamine Hagedorn*

Source: *Type 2 diabetes mellitus clinical practice guidelines for sub-Saharan Africa* [7]

Insulin preparations most used in the African setting are presented in Table 20.2.

Table 20.2 Insulin preparations used in Africa

Insulin preparation	Onset of action (min)	Peak action (h)	Duration of action (h)	Injections per day
Rapid-acting	10–20	1–2	3–5	Immediately before meals
Soluble	30–60	2–4	6–8	30 min before meals
Intermediate (NPH)	60–120	5–7	13–18	Once or twice
Lente	60–180	4–8	13–20	Once or twice
Biphasic mixture 30/70	30	2–8	Up to 24	Once or twice

Source: Type 2 diabetes mellitus clinical practice guidelines for sub-Saharan Africa [7]

Combination Therapy with Oral Antidiabetic Medications and Insulin

A combination of insulin and oral antidiabetic medications may be necessary to maintain blood glucose levels within optimal ranges. However, this combination therapy is used after failure of monotherapy with OAD, and insulin is required as a supplement to the OAD. An algorithm for the management of type 2 diabetes in Africa is shown below.

Algorithm for Type 2 Diabetes Mellitus Management

Step 1: (lifestyle modification)

1. Lifestyle changes: Diet, physical activity, smoking, and alcohol consumption cessation
2. Review in 3 months

   Note: If patient is unwell, with severe symptoms or pregnant, then refer to a tertiary hospital or admit patient and consider insulin therapy.

Step 2: (Oral monotherapy)

At follow-up visit after 3 months, if glycemic control is:

3. Adequate: Continue monitoring
4. Inadequate and patient is overweight: Start metformin at low dose, and increase three monthly as required until maximum dose reached
5. Inadequate and patient is not overweight: Start a sulfonylurea at low dose and increase every 3 months as required until maximum dose reached

Step 3: (Oral combination therapy)

At follow-up visit, if glycemic control is:

6. Adequate: Continue monitoring
7. Inadequate: Add another class of OAD, start at low dose, and increase every 3 months as required until maximum dose reached

Step 4: (Oral and insulin combination therapy)

8. At follow-up visit, if glycemic control is adequate, continue monitoring
9. Inadequate: Continue OAD and add bedtime intermediate acting insulin
10. Review in 3 months

Step 5: (insulin therapy in a secondary or tertiary service)

At follow-up visit in 3 months, if glycemic control is:

11. Adequate: Continue monitoring
12. Inadequate: More than once daily insulin is required, so refer to secondary or tertiary care

Adapted from type 2 diabetes mellitus clinical practice guidelines for sub-Saharan Africa [7]

Specificities of the Management of Ketosis-Prone Type 2 Diabetes

Ketosis-prone type 2 diabetes (KPD) is an atypical form of diabetes which is frequently seen in sub-Saharan Africa. Its management mandates some specific measures because of its dichotomic presentation: acute ketotic onset or relapse that resembles the clinical presentation of type 1 diabetes, further course that is similar to that of type 2 diabetes, and the high probability of near-normoglycemic remissions with risk of hypoglycemia if hypoglycemic agents are maintained in the treatment [22]. Though there is no consensual management strategy, expert opinion suggests the following [2]:

1. During the acute phase (onset or relapse)
   (a) Manage as any diabetes ketoacidosis
   (b) Assess autoantibodies to rule out type 1 diabetes
2. Early (first to second week) after the acute phase
   (a) Educate on hypoglycemia, adjustment of insulin doses and diet
   (b) Assess insulin secretion if possible
3. Few weeks after the acute phase
   (a) Close monitoring including close consultations and phone calls
   (b) Progressive insulin withdrawal, switch to oral antidiabetic drugs
4. Over months and years
   (a) Education on diet and physical activity, drug adherence, risk of hyperglycemic relapses
   (b) Standard follow-up similar to classical type 2 diabetes
   (c) Inpatient management in case of relapses

Prevention and Management of Acute and Chronic Complications of Diabetes

Prevention and Management of Chronic Complications

Populations of African origin are known to be more likely to develop microvascular complications of diabetes compared to the macrovascular complications of diabetes due to the limited access to adequate diabetes care and partly due to the high rates of hypertension in this population [23]. In most instances, the appearance of complications is the reason for patients seeking medical attention, making early detection of the disease very unlikely [24]. As a result of the higher frequency of microvascular complications of diabetes in patients in Africa, complications such as foot ulcerations, blindness, and renal failure are more frequent in these patients compared to complications resulting from large vessels involvement [25]. The African sociocultural context has a tangible impact on the management of these complications as some procedures such as amputations for chronic limb ulcerations are often unwelcomed [26]. The importance of patient education on the complications of diabetes and their management cannot be overemphasized.

As much as 50% of the patients with diabetes in the multicenter Diabcare study had their serum creatinine levels tested within the last year, with the highest percentages noted in Central Africa compared to East and West Africa. Of these patients tested, 54% had significantly raised serum creatinine levels [20]. Likewise, Central Africa compared to East and West Africa registered the highest proportion of patients tested for proteinuria in the last year [20]. These data show that diabetes complications are rare when adequately investigated for and therefore remain a major concern in the African setting.

With the appearance of complications, the risk of developing cardiovascular disease significantly increases, as well as disease-related mortality. Patients presenting with symptoms suggestive of a potential complication of diabetes should be referred to secondary or tertiary care for a proper assessment of complications. All associated complications of diabetes diagnosed following the full assessment should be promptly managed to prevent major sinister outcomes of diabetes that result in significant impairment such as amputation and blindness [7].

Management of Acute Complications of Diabetes

Poorly controlled diabetes can result in acute metabolic emergencies characterized by significant acute derangement in glycemic levels resulting in altered consciousness and even coma.

The reported acute metabolic complications of diabetic ketoacidosis and lactic acidosis, hyperosmolar states, and hypoglycemia are also common in Africa [25]. These life-threatening acute metabolic emergencies that require prompt life-saving interventions carry high mortality rates in Africa due to a constellation of reasons among which the late presentation at health facilities, delay in diagnosis, and even lack of insulin [7, 25]. Diabetes-related infections such as foot sepsis and hand infections have been proposed as acute complications of diabetes due to their high frequency and mortality in the African setting [25]. Clinicians should therefore be trained in diagnosing and managing these conditions.

Diabetic ketosis presents with elevated blood glucose levels, heavy and rapid breathing, raised serum, and urine ketones, with or without altered consciousness. Nonketotic hyperosmolar state that has a slower development of the hyperglycemic state presents with marked dehydration and uremia, with minimal or no ketonuria. The cornerstone of management of these conditions is prompt initiation of intravenous fluid resuscitation and gradual lowering of the blood glucose level using intravenous insulin [7]. This requires close monitoring of blood glucose levels, serum electrolytes, and creatinine levels, which is often challenging to implement. A protocol consisting of intramuscular insulin and rehydration was therefore proposed as an alternative to intravenous insulin use in the absence of appropriate monitoring facilities, based on its associated significant reduction in early deaths, simplicity, and inexpensive setup [27]. Hypoglycemia in revenge, characterized by extremely low blood glucose levels, often results from overdosing of diabetes medication and/or insufficient carbohydrate intake to maintain an adequate glucose level. In the African setting, this complication has been especially frequent with sulfonylureas agents [25]. Patients initiated on these agents and insulin should therefore be educated on the potential risks of hypoglycemia and how to prevent and/or manage it.

Management of Acute Diabetic Emergencies

Diabetic ketoacidosis and nonketotic hyperosmolar state

- Intravenous fluids: Minimum of 1 L in the first hour (if no contraindication)
- Insulin therapy: Short-acting insulin intramuscularly
- Immediate referral to an emergency unit (secondary or tertiary care)

Hypoglycemia

For conscious patient

- Oral glucose

For unconscious patient

- Intravenous fluids: 50% glucose bolus (40–50 mL) or 20% dextrose (100–150 mL) followed by 8–10% glucose if required
- Injectable glucagon
- Long-acting carbohydrate snack on recovery
- Continue intravenous dextrose 5–10% for 12–24 h as required
- Identify possible cause of hypoglycemia
- Review drug therapy and renal function and adjust antidiabetic treatment accordingly

Adapted from: Type 2 diabetes mellitus clinical practice guidelines for sub-Saharan Africa [7]

Management of Comorbidities

Management of diabetes entails managing associated comorbidities that tend to worsen the prognosis and overall quality of life of patients with diabetes by favoring disease progression to complications and target-organ damage. The principal comorbidities often associated with diabetes are cardiovascular risk factors and components of the metabolic syndrome such as hypertension and dyslipidemia. As much as 65% of patients with diabetes were being treated for hypertension, and 13% for hyperlipidemia in the Diabcare Africa study, with regional variations in these percentages [20]. Aggressive management of these comorbidities therefore forms an essential component of the management of diabetes in Africa. In individuals without these comorbidities, reducing their risk of developing these comorbidities is important. As with diabetes mellitus, the management of comorbidities is by both non-pharmacologic and pharmacologic means to achieve the desired treatment targets.

The main non-pharmacologic means for managing diabetes consist of lifestyle modifications and diet which also help in controlling the major comorbidities of diabetes such as hypertension and dyslipidemia. Failure of the non-pharmacologic means should prompt initiation of pharmacotherapy to control blood pressure, hyperlipidemia, and any other known co-comorbidities. Treatment should be individualized and special considerations taken for potential interaction between drug classes, diabetes, and antidiabetic medications. Regular monitoring of lipid profile and renal function of the patient should be ensured, and prompt referral to a specialist or for secondary/tertiary care should be

done in cases or poorly controlled comorbidities or suspicion of target organ damage [7].

Management of Comorbidities
Non-pharmacologic:

- Lifestyle modification
- Reduced salt and saturated fats in diet, regular physical exercise, weight loss

Pharmacologic:

- Antihypertensives (monotherapy, then combination therapy as required)
- Antihyperlipidemics

Treatment targets:

- Blood pressure
- Systolic blood pressure <130 mmHg (<125 if persistent proteinuria on dipstick)
- Diastolic blood pressure <80 mmHg (<75 if persistent proteinuria on dipstick)

Dyslipidemia:

- Total cholesterol <5.2 mmol/L
- LDL cholesterol ≤2.6 mmol/L
- HDL cholesterol >1.1 mmol/L
- Triglycerides <1.7 mmol/L

Interactions to consider:

- High-dose diuretics inhibit insulin release
- Beta-blockers may accentuate hypoglycemia
- Alpha-blockers may accentuate autonomic dysfunction
- B-beta-blockers and diuretics may worsen dyslipidemia
- ACE inhibitors may exacerbate hypoglycemia

Adapted from type 2 diabetes mellitus clinical practice guidelines for sub-Saharan Africa [7]

Follow-Up of Patients

Regular clinic follow-up is mandatory in the treatment and control of diabetes. The follow-up visits can range from weeks to months depending on the stage of the disease and other clinical and patient-related factors such as access to healthcare services. This has been a quite deficient arm of the overall diabetes care in Africa with patients often lost to follow-up due to several known and unknown reasons. Factors assessed at follow-up visits are shown in Table 20.3.

Monitoring of blood glucose control is best done by measuring the standard glycated hemoglobin levels (HbA1c). Unfortunately, the awareness and availability of this standard test are low in most African countries. As reported in the Multicenter Diabcare Africa study, access to HbA1c testing was as low as 47%, despite the variations across study centers [20]. There were, however, remarkable regional differences in the overall HbA1c awareness, being higher in the Central African countries compared to the West African countries. It is worth noting that in settings and centers where the HbA1c testing was available for monitoring of diabetes

Table 20.3 Factors assessed at follow-up visits

Initial visit	3-month visit	Annual visit
Primary level		
History and diagnosis	Relevant history	History
Physical examination	Weight	Physical examination
• Height and weight	Blood pressure	Biochemistry
• BMI	Foot inspection	(As at the initial visit)
• Waist and hip circumferences	Biochemistry	
• Blood pressure	• Blood glucose	
• Detailed foot examination	• Glycosylated hemoglobin	
• Tooth inspection	• Urine protein	
• Eye examination	Education advice	
– Visual acuity	Nutritional advice	
– Fundoscopy	Review therapy	
Biochemistry		
• Blood glucose		
• Glycated hemoglobin		
• Lipid profile		
• Creatinine		
• Blood electrolytes		
• Urine glucose		
• Urine ketones		
• Urine proteins		
Education		
Nutrition advice		
Medication if needed		
Secondary level		
All the above	All the above	As at initial visit
Eye examination		
ECG		
Biochemistry		
• Blood glucose		
• Glycosylated hemoglobin		
• Lipid profile		
• Creatinine		
• Blood electrolytes		
Tertiary level		
All of the above	All the above	All the above
Microalbuminuria		Microalbuminuria

Adapted from: Type 2 diabetes mellitus clinical practice guidelines for sub-Saharan Africa [7]

control, a low proportion of patients achieved their HbA1c targets [20]. An acceptable alternative to the HbA1c in the monitoring glucose control in Africa is the laboratory measurement of fasting and postprandial blood glucose levels. The use of urine glucose testing though might be the only alternative available in some resource-poor settings is not advised [7].

Current Challenges to Diabetes Management in Africa

Despite the progress made in the management of diabetes in Africa, much still needs to be done on the care of patients with diabetes in Africa. Diabetes is an expensive chronic disease not only for the health systems of countries in Africa but also for individual patients given the organization and financing of healthcare systems and payment of healthcare services by patients [3]. The barriers to adequate management of this chronic disease are:

- The unavailability of logistics for diabetes care
- Population awareness about diabetes and its management and complications due to nontreatment or poor compliance
- Poor glycemic control and late presentation to health facilities especially in type 1 diabetes [28]
- Scarcity of health personnel as a whole and those trained in diabetes care
- Access to medications due to their cost [4]

Africa that was initially plagued solely by the communicable diseases burden now faces a double disease burden, with the increasing number of patients with noncommunicable diseases. As such, the healthcare systems of countries in this part of the world are faced with the challenge of resource reallocation from the traditional communicable diseases such as malaria, HIV, and tuberculosis toward the management of chronic noncommunicable diseases such as diabetes [3]. This therefore becomes extremely challenging for healthcare systems of these countries which by default are more adapted to managing acute conditions rather than chronic diseases [29].

As with other chronic conditions, cost stands out as a principal determinant of access and adherence to treatment. Access to antidiabetic medication therefore stands out as one of the major challenges faced by patients in Africa [25]. The lack of universal health coverage in most African countries implies out-of-pocket payments are the main way through which individuals pay for healthcare services, making access to treatment difficult given the high proportion of people living below the poverty threshold. This is particularly the case with insulin-based treatment of diabetes which is not always affordable when available [3]. As such, the prognosis of this disease in Africa has not often been satisfactory as in other parts of the world [30, 31]. In 2005, insulin was estimated to cost between $4.30 and $4.60 per 10-mL U100 vial, in Mozambique and Zambia, when bought by the national health systems. Insulin was even more expensive when bought by individuals from private wholesalers [3].

Other more specific problems faced with regard to the management of type 1 diabetes mellitus are the quantification of insulin needs, the storage of insulin under optimal temperature conditions, and timely ordering of medication stocks to ensure permanent availability at all levels of patient care [3].

Population awareness and education about diabetes is a major factor. Many people living with diabetes still resort to unconventional and alternative treatment means such as traditional healers who are generally unlikely to refer patients back to healthcare facilities [4, 32]. There is a need to conduct operational research on such alternatives with a bid to define their potential role in the management strategy of diabetes. Knowledge about diabetes, its complications, and how to manage it is still low [33]. This makes the control of this chronic disease difficult in Africa. This lack of awareness is not limited just to the patients and their caregivers but has been reported to extend to healthcare providers as well [34], with reported instances of coma as a result of diabetes being diagnosed as cerebral malaria or HIV/AIDS, all favored by the lack of appropriate diagnostic facilities [3]. Despite the adoption of the westernized lifestyles that could increase risk of developing diabetes in Africa, the sociocultural practices in this part of the world have not made adequate allowances for the accompanying practices that could reduce disease risk such as adequate physical activity and healthy diet [32]. This is even worsened by local perceptions of the African setting such as the fact that obesity is an indicator of affluence and good living [11]. Despite all the challenges and barriers to the effective management of diabetes in Africa, it is worth noting that there exist considerable within-country differences, with urban regions having more satisfactory systems in place to manage diabetes than the rural areas.

Newer Approaches to Diabetes Management in Africa

Newer approaches to diabetes management are increasingly being implemented in Africa such as the social support and self-management of diabetes that are currently in use in developed countries. Several countries in Africa have now created a national diabetes registry and diabetes associations and are implementing national diabetes programs alongside

other primary healthcare programs to cater for patients with this disease. The setting up of diabetes clinics across countries through joint efforts from national diabetes associations and ministries of health is consistently adopted due to their efficiency in disease management [35].

These approaches and programs have been aimed at improving patient education and awareness about diabetes, patient empowerment with regard to diabetes management, health personnel training, medication supply, diagnostic facilities, and overall improvement in healthcare systems across the continent [3].

Patient education and empowerment aims to educate patients on what diabetes is, how to take care of themselves to reduce their risk of having diabetes, and how to self-monitor their glycemia and adopt healthy lifestyles to reduce the risk of developing complications. The diabetes self-management support provided should be patient-centered, individualized, integrate cognitive-behavioral interventions, and involve the patient as much as possible in the decision-making process [10]. Patients should also be provided with the resources to be able to undertake self-care [7]. The adoption of less costly preventive measures such as physical activity and more precisely aerobic exercise known to improve metabolic and anthropometric parameters of patients with diabetes mellitus should be encouraged.

Points to be covered in a self-assessment education of diabetes patients are covered in Table below [8].

Basic Knowledge of Diabetes

- Basic knowledge of diabetes.
- Importance of good comprehensive control and methods to achieve this.
- Insulin injection techniques and sites of injection.
- Self-monitoring of blood glucose.
- Recognition and management of acute and chronic complications.
- Foot care.
- Smoking cessation and responsible alcohol use.
- Preconception care.
- Pregnancy: preparing, managing diabetes during pregnancy, and appropriate postnatal care.
- Psychosocial issues, stress management, and coping skills.
- Training of caregivers and family of people with diabetes.
- Managing diabetes emergencies.
- Importance of an identification disc or bracelet.
- Children with type 2 diabetes should be referred for specialist assessment and diabetes education.
- Management of elderly patients:
  - Assess knowledge and understanding of diabetes.
  - Evaluate ability to learn and apply new self-care skills.
  - Assess nutrition and physical activity.
  - Address polypharmacy and comorbidities.
  - Assess for cognitive dysfunction, depression, and physical disability.
  - Address quality of life versus life expectancy.

Adapted from the 2012 SEMDSA Guideline for the Management of type 2 Diabetes [8]

Healthcare providers should be trained on diabetes as a chronic disease and its management. They should also be trained on how to disseminate this information to the population that makes use of the health facilities and through other means of community engagement and communication [33].

Task shifting in the care and management of patients with diabetes is also gaining grounds in sub-Saharan Africa. There are reports of the successful implementation of nurse-led diabetes care [36, 37]. This has turned out to be cost-effective and has helped in solving the shortage of doctors treating patients with diabetes mellitus [38].

Concerning improving diagnostic facilities and medication supply, standardized means of assessing blood glucose levels should be available at the various levels of patient referral of the health system. Medications for treatment should be made available at all times through improvements in the supply chain dynamics of antidiabetes medications, and these medications have to be made affordable for patients [3].

Another important component of the newer approaches to diabetes management in Africa is the implementation of monitoring of care system, whereby, the quality of care offered to patients is periodically monitored to identify deficiencies and correct them as appropriate [7].

Above all, the availability of adequate data on disease burden and current level of treatment coverage remains fundamental to assessing the actual progress of the management of this disease and planning on measures to improve diabetes-related mortality and morbidity [28]. Likewise, extensive research should be funded to investigate on the presentation and specificities of this condition in this part of the world [28]. This will demand enormous coordinated actions between key stakeholders, ministries of health, and both government and nongovernmental organizations. A multidisciplinary approach to diabetes prevention and treatment is therefore necessary for effective

management of diabetes in Africa, with the involvement of all key stakeholders both at patient and community levels [3, 5, 28].

At the international level, the African regional branch of the International Diabetes Federation, through the African Diabetes Declaration, has summoned governments and agencies involved in diabetes care in Africa to uphold standards of diabetes care with regard to prevention, early detection, and availability and affordability of treatment [3].

The International Insulin Foundation has summarized adequate diabetes management in Africa in 11 keys points [3].

Diabetes Management in Africa

- Organization of the health system
- Prevention
- Data collection
- Diagnostic tools and infrastructure
- Drug procurement and supply
- Accessibility and affordability of medicines and care
- Training and availability of healthcare workers
- Adherence issues
- Patient education and empowerment
- Community involvement and diabetes associations
- Positive policy environment

Adapted from Diabetes care in sub-Saharan Africa [3]

Concluding Remarks

- The management of diabetes in Africa has significantly improved over the decades with management taking a more holistic approach.
- There are still limited contextualized guidelines specific to the management of diabetes in Africa, as many countries still rely on guidelines essentially used in developed countries.
- Treatment cost and medication availability remain as major barriers to effective treatment in Africa.
- The role of new drugs such as GLP-1 receptor agonists or sodium-glucose cotransporter 2 (SGLT2) antagonists is worth evaluating.
- A multidisciplinary approach to diabetes prevention and treatment is necessary for effective management of diabetes in Africa.

Multiple Choice Questions

1. Measures aimed at early detection of disease in affected individuals are known as:
   (a) Primary prevention
   (b) **Secondary prevention**
   (c) Tertiary prevention
   (d) Treatment
   (e) Management
2. The following are major objectives of the management of diabetes, except which one:
   (a) **Bring down HbA1c level below 7% for all.**
   (b) Early detection of disease in affected individuals.
   (c) Improve the quality of life of patients with diabetes.
   (d) Prevent disease progression to complications.
   (e) Empower patients and encourage self-care practices.
3. All the following apply to the management of ketosis-prone type 2 diabetes, except which one:
   (a) Patients usually require insulin at onset.
   (b) Patients may be insulin-free for years.
   (c) **Patients are insulin-dependent for life.**
   (d) Patients may keep an excellent glucose control without any treatment.
   (e) Patients are in high risk of hypoglycemia during the remission period.
4. Management of diabetes is centered on which of the following:
   (a) Early screening and diagnosis of diabetes
   (b) Management of blood glucose
   (c) Management of comorbidities
   (d) Prevention and management of acute and chronic complications of diabetes
   (e) **All of the above**
5. Which of the following is not a routine pharmacologic management option for diabetes?
   (a) Insulin therapy
   (b) **Vitamins and minerals**
   (c) Biguanides
   (d) Sulfonylureas
   (e) Meglitinides
6. Medical nutrition therapy recommends one of the following except:
   (a) Increasing daily water intake and having meals at regular times daily
   (b) Variety of vegetables and fruits excluding fruit juices
   (c) **Restrictive diets consisting of protein-rich, carbohydrate-free, and fat-free items**
   (d) Limiting daily fats consumption to <35% of the total energy intake

(e) Reducing dietary salt intake to control blood pressure (<2300 mg/day)

7. Which of the following oral antidiabetic class is recommended as the first line for outpatient care of type 2 diabetes?
   (a) Insulin
   (b) Sulfonylureas
   (c) Meglitinides
   (d) **Biguanides**
   (e) Thiazolidinediones
8. Well-known barriers to the management of diabetes in Africa consist of all of the following except:
   (a) The unavailability of logistics for diabetes care
   (b) Population awareness about diabetes and its management and complications due to nontreatment or poor compliance
   (c) **The use of oral antidiabetic agents instead of insulin in patient with diabetes**
   (d) Late presentation to health facilities
   (e) Access to medications due to their cost
9. Which of the following side effects of antidiabetic treatment is a major barrier to management?
   (a) Gastrointestinal side effects
   (b) Cardiovascular side effects
   (c) Skin side effects
   (d) Hematological side effects
   (e) **Hypoglycemia**
10. The following assessments are part of the annual evaluation of patients with diabetes, except which one:
   (a) **Blood urea nitrogen**
   (b) Urine dipstick
   (c) Serum creatinine
   (d) Electrocardiogram
   (e) Lipid profile

Answers

1. Secondary prevention consists of methods aimed at identifying patients with disease early before the progression of the disease, as opposed to primary prevention which entails adopting measures to reduce the risk of developing the disease, and tertiary prevention which entails treating the disease to reduce mortality and morbidity.
2. This question aims at raising the awareness of physicians taking care of diabetes, on the fact that people living with diabetes should not be restricted to HbA1c level. Targeting HbA1c level below 7% is indeed important; it is part of the objective "prevent disease progression to complications." Also, HbA1c target should be individualized.
3. Ketosis-prone type 2 diabetes is characterized by an acute ketotic onset that usually requires insulin therapy. This phase is usually followed by a long-term insulin-free remission, during which patients may keep an HbA1c level below 6.5% even without any treatment.
4. Management of diabetes entails preventing disease occurrence, management of the blood glucose level, preventing the progression of the disease to complications, and preventing or managing its acute and chronic complications in affected individuals.
5. Body needs in mineral and vitamins are generally obtained from a regular balanced diet. Mineral and vitamin supplements are not routinely administered to patients with diabetes unless they have other conditions requiring their supplementation such as in lactating pregnant women. An affluence of food supplements—usually merely made up of vitamins and minerals—in Africa over the past two decades has contributed in disturbing diabetes management. The marketing message conveyed by companies selling these products is that food complements can "cure" diabetes and many other epidemics. These food supplements are not recommended in diabetes management.
6. Medical nutrition therapy which is the first-line treatment of diabetes mellitus consists of all the options mentioned in the question except restrictive diets consisting of protein-rich, carbohydrate-free, and fat-free items which are no more recommended due to no proven long-term benefit. Restrictive diet is not recommended and may be dangerous.
7. Metformin, which is a biguanide, is recommended by most guidelines as the first-line pharmacologic agent in the management of type 2 diabetes.
8. Even though oral antidiabetic agents are the first-line pharmacologic options to use in patient with diabetes, there are instances in which insulin is preferentially used. Nevertheless, using oral antidiabetic agents instead of insulin is not reported as being one of the reasons for suboptimal management of diabetes in Africa.
9. Hypoglycemia is the major side effect of antidiabetic treatment. Fear of hypoglycemia by patients or healthcare personnel is a factor for nonadherence to treatment and therapeutic inertia.
10. Blood urea nitrogen (BUN) is not part of the routine assessment of diabetes. Routine BUN test is a waste of money. The other tests stated in the question are mandatory as they help identify chronic complications or cardiovascular risk factors associated with diabetes.

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Part IV

Basic Components of Management: Patient Centeredness, Evidence-Based Medicine and Outcomes—Challenges for Implementation

The Patient-Centered Medical Home, Primary Care, and Diabetes

21

Joel Rodriguez-Saldana

The sick suffer enough We must avoid adding insult to injury by denying them a proper role in determining their future

Jerome P. Kassirer, M.D.

Introduction

Current models of health care continue to be designed to address every type of health problem from an acute disease approach, based on episodic face-to-face interactions between healthcare providers and patients; this approach does not address the multiple needs of patients with chronic diseases like diabetes [1]. In contrast, participation of patients has become increasingly important; they are assuming new roles as active agents, managers, and producers of their own health; involvement of patients is a new way to understand the relationship between patients, health professionals, and health systems, not only to recognize that they are the main responsible of their health control but they also have an undeniable influence in policy planning [2]. Healthcare providers should ensure to meet the information needs of patients because their perceptions of quality of care and quality of life are associated with the physicians' ability to transfer key information to them [3]. The professional ideal of the physician-patient relationship claims that doctors are directors of care and decide about treatment; the patient's principal role was to comply or obey "doctor's orders" … while the patient (supposedly) had only a minimal role in making decisions [4]. We have come a long way from the paternalistic view of medicine that excluded patients from discussions about their own health [5]. The enhanced capacity to address patients' needs increases loyalty and persistence, reduces complaints, increases the efficiency, and is also profitable [6]. Improvements in health care can be accelerated and evaluated developing patient-based measurement systems able to provide direct measures of success and failure, strengths and weaknesses, improvements, and declines in the provider's capacity to produce the desired health outcomes [7]. In sharp contrast with these realities, examples of doctors who reject patients not because of time limitations, but on far more questionable grounds, including sexual orientation, ethnicity, or specific health problems such as HIV infection, diabetes, and obesity, have been described and highly publicized as causes of rejection [8]. One of the drivers of the health disparities observed in diabetes is discrimination; discrimination is associated with decreased feeling of patient-centeredness and increased dissatisfaction with care [9]. Discrimination affects health through psychological and physiological stress responses; it is associated with loss of trust, lack of adherence, and poor diabetes management; reduces the use of diagnostic tests including A1c testing and cholesterol checks, using clinical services such as eye examinations and immunizations; and produces dissatisfaction with care [9]. Patient dissatisfaction is significantly associated with lower general dieting, higher HbA1c levels, and lower mental quality of life component [10]. The results of a study published by Cykert and colleagues reinforce a need for patient-provider communication that is inclusive, eliminates perceptions of discrimination and bias, increases patient-centeredness, and improves overall clinical care [9]. Physician empathy is significantly associated with clinical outcomes, including lower rates of acute metabolic complications. Empathy should be considered an important element in patient care and a significant factor of physician competence [11], but in the real world, coverage denial, lack of access, or delayed access to health care are highly preva-

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lent [12]. In the United States, for example, Pearson reported a 7% rate of denial of coverage within a mixed model HMO [12]. In countries like Mexico, the percentage of out-of-pocket medical expenses, even in recipients of social security, has been estimated to be as high as 75% [13]. Denial of coverage or denial of services is associated with lower ratings of quality of health care and less trust on physicians [12]. A report from a nationally representative sample showed that patients with the highest levels of satisfaction had lower rates of visits to emergency departments, while people at the lowest levels had higher rates of hospitalization, greater expenditures in medications, and higher risks of mortality [14]. Patient-centeredness is an important issue in health care; it is highly dependent on patient's values and preferences, the professionals' behavior, and the interactions of both and seven key elements: (1) uniqueness, (2) autonomy, (3) compassion, (4) professionalism, (5) responsiveness, (6) partnership, and (7) empowerment [15]. Health beliefs and the self-reported capacity to adhere to treatment regime or to follow general advice are consistently predictive of glycemic control and reduction of cardiovascular risk factors [16]. The crucial role of patients and their families on the intermediate- and long-term outcomes is an essential component of diabetes management. Diabetes has become a representative model of the patient-centered medical home and should be properly addressed in clinical practice.

Milestones of Patient-Centered Care

Western health systems were initially dominated by a paradigm that considered "diseases" as basic elements of pathology. Since the seventeenth century, diseases were considered as functional or structural abnormalities of cells or body organs, with each abnormality added in linear fashion to the extent of illness. Barbara Starfield claimed that "medicine is still practiced this way…in this outdated scheme there is no room to recognize that diseases are not distinct biological entities that exist alone and apart from the person [17]."

The pathological model of disease was challenged in recent decades by a new form of clinical practice that stresses the centrality of the person (not the patient), her or his risk factors and personal priorities, and the role of medical surveillance to understand health and illness. In 1971, DC Taylor brilliantly described three components of sickness: (1) diseases, referring to abnormalities in diagnostic tests; (2) illnesses, unique combinations of symptoms and signs in an individual; and (3) predicaments, the personal, social, and economic consequences of being sick [18]. The paradigm of the pathological model of disease claimed that if mankind could master nature through science, every clinical problem would have a single explanation and solution. Nevertheless, a "whole patient"-oriented view of disease is more accurate and more equitable than a disease-oriented view [18]. Medical care must evolve to meet the healthcare needs of patients in the twenty-first century; clinical decision-making should focus on the attainment of personal goals, identification, and treatment of all modifiable biological and non-biological factors, instead of solely relying on the diagnosis, treatment, and prevention of individual diseases [19].

Primary Care as the Site of the Medical Home

A new paradigm in health care was announced by Freyman in 1989, in which the focus of health care would have shifted to the community [20]. Diagnosis and treatment would be managed in ambulatory settings including home, and the hospitalized fraction of the population needing medical care would be smaller…primary physicians would be the key personnel of vertically integrated systems to become the first contact of patients and would be responsible to coordinate services; to provide continuing, comprehensive, and up-to-date medical care; and to refer "the relatively few" who need the services of specialists [20]. These visionary predictions met strong resistance in many countries; reasons include the natural resistance to innovate, the perception of this innovative model as a threat to current interests, particularly economic, of physicians and health organizations, and perceptions of low value by providers of "solutions" of high cost [21]. Although some nomadic patients prefer to navigate through episodic encounters with emergency departments and specialists, most people want a medical home, in which responsibility of care and care coordination resides in the personal medical provider working with a healthcare team according to patient's needs and including specialists, midlevel providers, nurses, social workers, care managers, dietitians, pharmacists, physical and occupational therapists, family, and community [22]. Primary care, in which physicians address most of the patients' healthcare needs through their lifetime, was conceived to become the medical home [23]. One of the first descriptions of the attributes and the roles of primary care was made by Scheffler and colleagues in 1978 and included (1) accessibility, (2) comprehensiveness, (3) coordination, and (4) continuity, delivery by accountable providers of personal health services associated with the care of the whole person, rather than of particular illnesses, and distinguished from other levels of health care by the nature of the services, not by the particular training of the provider (i.e., not necessarily provided by physicians [23]). In 1998, Barbara Starfield described the four essential functions or major features of accountability of the primary care medical home [24] (Table 21.1):

Table 21.1 Attributes of primary care

Function	Description
1. Accessibility, first contact, gatekeeping	A place of easy access for health care; a gate to start receiving care from health professionals, nurses, or physicians
2. Comprehensiveness	Arrange and provide the full range of health-related needs including preventive, acute, chronic, rehabilitative, and palliative services
3. Sustained, longitudinal care	Dealing with changes in the health status of individuals or groups of people over years from a regular source of care, in one place, by an individual or team
4. Coordination	Harmonized referral: integration of all types of care, regardless of provider, including specialists and hospitals

Modified from [24]

Roots and Milestones of Patient-Centered Care

Historically, excellence in western medicine was based on the application of anatomy and physiology on the care of patients, but many years ago, this idea was challenged [25]. In 1882, Nothnagel in Vienna claimed that "medicine is about treating sick people and not diseases," in 1892 Sir William Osler declared that "It is more important to know what sort of patient has a disease than to know what kind of disease has the patient" and in 1926 Crookshank pointed out that "since the origins of the clinical method in ancient Greece, there have been two meanings of diagnosis: to diagnose a disease and to diagnose a patient [26–28]." The term "patient-centered medicine" was introduced by Balint and colleagues in 1970 in contrast to "illness-centered medicine [29]," and patient-centered medicine had its roots in 1967, when the American Academy of Pediatrics (AAP), under the leadership of Calvin Sia, introduced the term "medical home" in the book *Standards of Child Health Care* to describe an approach to taking good care of children with special care needs [30]. According to Reach and McWhinney, the idea of person-centered or patient-centered care is a "rediscovery [26, 27]." The doctor-centered model is the doctor's attempt to interpret the patient's illness in terms of medical explanations in order to assign the patient's illness to one of conventional disease categories [26]. From this perspective, success depends on the accurate classification of illness, the capacity to link the patient's symptoms and signs with organic pathology and to identify causal agents, and its etiology [26]. These two approaches are clearly different; they represent two ways of thinking, two attitudes to life, two different mental sets, and probably two personality types for practicing medicine [26]. Disease-centered recommendations do not address what matters most to patients, who have different health priorities… patient's goals and preferences are rarely translated into actual care decisions [31].

The Link Between Primary Care and Patient-Centered Care

Primary care probably dates back to the Dawson Report published in the United Kingdom in 1920 which introduced three levels of care: (1) primary, (2) secondary health centers, (3) teaching hospitals, which are still the basis of the pyramidal regionalization of health services [32]. Primary care found its roots in the 1960s and 1970s when the vertical approach to health care and the efforts to *transplant* hospital-based healthcare systems to developing countries in the absence or lack of emphasis on prevention were criticized [33]. At the 1976 World Health Assembly, Halfdan Mahler proposed the goal of "Health for All by the Year 2000," which became crucial in the history of primary care, and that would be confirmed at Alma Ata in 1978 [33]. As already mentioned, the AAP defined the medical home as the repository of medical records for chronically ill children and expanded the definition to include primary care accessible, continuous, comprehensive, coordinated, family centered, and culturally effective [34]. In 1978, the World Health Organization incorporated several concepts currently described as part of the Patient-Centered Medical Home (PCMH) at the Primary Care Conference of Alma Ata in 1978, including (1) access and continuity to care, (2) comprehensiveness and integration of care, (3) patient education and participation, (4) team-based care, and (5) public policies supporting primary care [35]. Since Alma Ata, promotion of primary health care stressed the need to address the health needs of all people and to recognize family physicians as the primary providers of health care albeit disillusionment about its real contribution to health improvement still persist [36]. Achievements continue to fall short of expectations; it is time to launch renewed efforts to strengthen health systems and integrate primary health care [36]. The "missing link" to translate the principles of Alma-Ata from idealism to practical effective public strategies has been the incapacity of health systems to integrate personal and public health, but the challenge continues to be shifting personal health care at the expense of population health [36]. By stating that health is a fundamental human right, the declaration of Alma-Ata was a landmark in public health [37]. In 2017, a similar declaration was made for experts in the field of diabetes. The Berlin Declaration called for early action to address the dangers of the type 2 diabetes pandemic in accordance with the World Health Organization's vision to decrease the expected rise in type 2 diabetes and obesity by 2025 [37–39]. The Berlin Declaration involves prevention and management

policies, including encouragement of primary care physicians to prioritize screening "despite having to address multiple health problems during short consultations [39]." Unless these limitations are realistically addressed devoting additional resources and overhaul of health systems to increase the time for medical visits and multidisciplinary care, the status quo of primary diabetes care will prevail.

The Paradox

It has been shown that primary health care contributes to reduce the adverse impact of social inequalities of health and is more effective to achieve better health outcomes, at lower costs, than systems oriented to disease management and specialized care [40]. The turning point in primary care is to recognize the inescapable fact that patients with chronic conditions self-manage their illness, and while physicians are experts about diseases, patients are experts about their lives [40]. Traditional views regard physicians and health professionals as experts, with patients bringing only their illness to receive and obey medical orders. In chronic diseases like diabetes, a paradigm shift has emerged: patients are their main caregivers ("the experts of their disease" in the words of Elliot Joslin), and the role of physicians is as supporting consultants [41]. The literature about the benefits of primary care has shown greater effectiveness, efficiency, equity, and understanding of the mechanisms by which its benefits are achieved [41]. The following attributes in combination produce better services: (1) greater first contact access and use, (2) more continuing person-focused care, (3) greater range of services, and (4) coordination [42].

Primary care rapidly evolved but also became an endangered species: doctor's duties changed, influenced by advances in medical knowledge and technology, the increasing use of computers, handheld devices, and electronic records, and the growing trend to track and measure clinical data [43]. The pressure on physicians to accomplish multiple goals has intensified worldwide; many patients describe their doctors as hurried and unresponsive, while nurse practitioners are perceived more willing to take time to talk to patients and answer questions; most of the time, physicians' days are spent on administrative tasks, paperwork, and data entry [43]. Overwhelmed by large patient workloads, many primary care practices are performing poorly: patients are interrupted after 23 s trying to explain their problems to a physician, 50% of patients leave office visits not understanding what the physician has told them, and evidence-based care is provided on a limited basis [44]. Two possible solutions are a very difficult one, devoting more time per patient, and a more feasible one, pioneered by Bodenheimer and colleagues: reorganizing primary care as a team-based endeavor, in which many functions currently in the hands of physicians are provided by other staff members, including nurses or medical assistants [45].

Primary care physicians are central and core components of any high-quality healthcare delivery system [46]. The Academy of Clinical Excellence (MCACE) at Johns Hopkins University states that clinical excellence involves achieving distinction in six plus-one areas related to patient care [46]:

1. Communication and personal skills promoting successful physician-patient relationships
2. Professionalism and humanism supporting development and maintenance of strong physician-patient relationships
3. Diagnostic acumen, the "science and art" of using information gathered from the history and physical examination to make the correct diagnosis
4. Skillful negotiation within the healthcare system, to overcome fragmentation with providers, sites of care, and record systems
5. The ability to find, interpret, and apply information to solve clinical problems
6. A scholarly approach to clinical practice to ensure that physicians remain informed about the best practice
7. Plus a passion for patient care [46]

Challenges to Implement the Patient-Centered Medical Home

In the medical home, responsibility and care coordination reside in the patient's personal medical provider working with a healthcare team and including specialists, midlevel providers, nurses, social workers, care managers, dietitians, pharmacists, physical and occupational therapists, families, and communities. Patient-centered medical homes and primary care are at a crossroads in many countries: family medicine appears to be largely devalued as a professional activity among medical students, who are more interested into specialty care, and primary care physicians are discouraged and even leaving practice [47, 48]. In most medical schools, students spend time in the offices of primary care physicians, where they observe the reality of this type of practice and gain insight into the challenge of caring for patients with a wide range of conditions, including chronic diseases [49]. When they observe patients with chronic diseases like diabetes who were hospitalized because of inadequate treatment, medical students cannot help but notice how little attention is devoted to avoid hospitalization through better outpatient management and the scarcity of team-based, patient-centered models for chronic disease [49]. Time pressures, chaotic work environments, increasing administrative and regulatory demands, an expanding knowledge base, fragmentation of

care delivery, and the high expectations placed on primary care are multiple contributors to the strain [21]. Burnout is an additional threat to primary care; high levels of emotional exhaustion are endured by staff and clinicians, resulting in low professional competence, cynicism, and denial [50]. Tight team structures and greater team cultures are associated with less clinician stress and burnout [51]. Under the leadership of Thomas Bodenheimer, the Center for Excellence in Primary Care at the University of California in San Francisco has clearly and since a long time demonstrated that the current practice model of primary care is unsustainable [52]. They described barriers and limitations to deliver high-quality primary care and the following solutions: (1) expanding the role of health assistants to deliver pre-visit and post-visit activities; (2) adding capacity, sharing care with other team members; (3) reducing or eliminating time-consuming administrative work; (4) prescription renewal to save time; (5) return tasks corresponding to receptionists, pharmacists, and nurses; and (6) improving team communication and functioning within a systems-approach redesign [52, 53]. In the face of a growing gap between the supply and demand of primary care, the practice should provide prompt access to high-quality care that maximizes patient's experiences, minimizes healthcare costs, makes primary care more attractive for physicians, and engages nonphysician members in the care process [54]. Improvements in the delivery of high-quality primary care result in higher proportions of patients achieving targets of HbA1c, triglycerides, and high-density cholesterol and significant reductions in HbA1c, blood pressure, LDL cholesterol, triglycerides, body mass index, reducing clinical inertia and the incidence of complications [55]. Delivering high-quality primary care for patients with diabetes is feasible but requires reinforcements in structure and process that most health systems across the world do not perceive or are unwilling to carry out. Primary care is the backbone of health systems and countries aspiring to universal, effective health coverage; a strong primary care system is the essential building block [45].

Transitioning from Primary Care to the PCMH

Patient-centered medical homes represent an updated model of primary care that recognizes and rewards the diverse but necessary activities for a population of patients [48]. Actions taken by policy-makers and payers to recognize the essential role of primary care physicians such as Medicare and Medicaid payments under the Affordable Care Act in the United States were tempered by continuing divisions between supporters of primary care and specialty care over the relative value of their services and the decreasing interest of medical school graduates for primary care [56]. Most developed nations assure access to primary care physicians who are paid based on guidelines and outcomes established by consumers and providers, but others have created and nurtured the perception that universal access to care is too expensive and unaffordable [56]. The National VA Primary Care Survey on Primary Care directors identified 16 moderate-to-extreme challenges to implement patient-centered medical homes, including access, preventive care screening, chronic disease management, "challenging medical conditions," mental health, special populations, coordination of care, and informatics [45]. A primary care practice that wants to deliver health care effectively must interact with patients where, when, and how they want to be served [54]. According to Berry et al. and Tayloe, its building blocks include physical and remote visits [57, 58]. The former include office visits with physicians and health professionals and visits to satellite clinics; remote practice involves at-home visits, telemedicine, and web-based services [58]. Additionally Tayloe described ten key components of the PCMH: (1) a visionary leadership with an outcome approach to health care, (2) a team of providers who are able to provide state-of-the art care, (3) minimization of unnecessary emergency and hospital admissions, (4) integration of hospital and office care, (5) business expertise of physicians and staff, (6) user-friendly electronic medical records, (7) physicians and staff trained and able at implementing quality improvement projects, (8) community-based coordination, (9) support from private and public third-party providers, and (10) a clear understanding of the community needs [58].

Patient-Centered Care Defined

Table 21.2 shows definitions of patient-centered care [59–61]:

Table 21.2 Evolving definitions of patient-centered care

Year	Author(s)	Definition
2001	Institute of Medicine [59]	Health care that establishes a partnership among practitioners, patients, and their families to ensure that decisions reflect patients' wants, needs, and preferences and that patients receive the required education and support to make decisions and participate in their own care
2010	Epstein et al. [60]	Personal, professional, and organizational relationships; an approach to care perceived as the right thing to do, in order to understand a series of outcomes, including feeling understood, trust, or motivation for change
2012	Valko et al. [61]	Team-based, comprehensive primary care, involving multiple professionals, including physicians, assistants, nurses, social workers, pharmacists, and behavioral specialists. Not just a place but a model of health care designed to reliably and reproducibly implement the core functions of primary care

Attributes of Patient-Centered Care

Over three decades, several visions about the attributes of centered care have been described, each one with different, enriching patient perspectives (Table 21.3) [62–67]:

The origins of these dimensions are variable; for example, the principles proposed by the Picker Institute were developed from surveys to evaluate patients' experiences with many clinical conditions and in every setting of health care, "with the dream to transform health

Table 21.3 Attributes of patient-centered care

Year	1983	1993	2005	2007	2010	2010
Authors	Levenstein et al. [62]	The Picker Institute [63]	Davis et al. [64]	American Academy of Family Physicians [65]	Battersby et al. [66]	Epstein et al. [67]
Attributes or principles	1. Entering the patient's world to see the illness through the patients' eyes	1. Respect for the patient's values, preferences and manifest needs	11. Superb access to care	1. Enhanced access and continuity	1. Brief targeted assessment	1. Healing personal relationships between clinicians, patients, and family members; bridging demographic, social and economic differences between clinicians and patients
	2. Invitation and facilitating openness by patients	2. Coordination and integration of care	12. Patient engagement in care	2. Identification and management of patient populations	2. Evidence-based information to guide shared decision-making	2. Teamwork from a coordinated community of healthcare professionals, including preparations before office visits and eliciting patient's concerns early in the visit
	3. Main objective: allowing patients to express all the reasons of visit	3. Information, communication, and education	13. Clinical information systems supporting high quality of care, practice-based learning and quality improvement	3. Planned and managed care	3. Nonjudgmental approach	3. Shared tailored information, shared deliberation considering patient's needs and preferences, care beyond informed consent or treatment
	4. Aim: to understand each patient expectations, feelings, and fears	4. Physical comfort	14. Care coordination	4. Self-care support and community resources	4. Collaborative priority and goal setting	
	5. Key aspect: allowing as much possible the flow from the patient	5. Emotional support, alleviating fear and anxiety	15. Integrated, comprehensive care and smooth information transfer	5. Track and coordinated care	5. Collaborative problem-solving	
	6. Crucial skill: be receptive to verbal and nonverbal cues from patients	6. Involvement of family and friends	16. Ongoing, routine patient feedback	6. Measurement and improved performance	6. Self-management support by diverse providers	
		7. Transition and continuity			7. Self-management interventions by diverse formats	
					8. Patient self-efficacy	
					9. Active follow-up	
					10. Guideline-based case management for select patients	
					11. Linkages to evidence-based community programs	
					12. Multifaceted interventions	

Table 21.4 Joint Principles of the Patient-Centered Medical Home (PCMH) integrating behavioral health care

Principle	Description
Personal physician	To guarantee that each patient has an ongoing relationship with a personal physician trained to provide first contact, continuous and comprehensive care, with a whole person orientation
Physician-directed medical practice	Physicians lead the PCMH, supported by a team of health professionals to integrate the physical, emotional, and social aspects of the patient's health needs
	Facilitative leadership involves shared responsibility, seamless teamwork, honoring the unique abilities of each member, and enabling members to work to their full potential
Orientation to the whole person	Responsibility to provide all the patient's healthcare needs and arrange care with other qualified professionals, including care for all the stages of life, acute care, chronic care, preventive services, end-of-life care, psychosocial dimension, and resulting behavior changes in the provision of all the patient's healthcare needs
Coordinated and/or integrated care across all the healthcare system and the patient's community	Assurance that patients receive the indicated care when and where they need and want it. Avoid fragmentation and separation of primary from behavioral health care
	Shared registries, medical records, decision-making, revenue streams, and responsibilities. Clarification of real and perceived barriers to communication and regular sharing of information
Quality and safety as hallmarks	Support the attainment of optimal, patient-centered outcomes by care planning processes driven by partnerships between physicians, behavioral health professionals, patients and their families
	Support from evidence-based medicine and clinical decision support tools
	Accountability for continuous quality improvement and performance measurement
	Active participation of patients in decision-making and feedback to ensure that their expectations are met
	Appropriate use of information technology to support optimal patient care, performance measurement, patient education, and enhanced communication; incorporate behavioral health, mental health screening, and health outcomes
	Recognition by nongovernmental entities to document the capacity to provide patient-centered services and behavioral care within the medical home model
Enhanced access	Access to patients, families, and physicians to medical and behavioral care through collaboration, shared problem-solving, flexible team leadership, and enhanced communication
Appropriate payment	Recognition of the added value of behavioral health care; payment in addition, not separate from primary care. Pay per-member and per-month primary care capitation

Modified from [65, 68]

care systems into a real system that provides effective and compassionate care for everyone [63]." The American Academy of Family Physicians and associates developed their principles based on the chronic care model and the medical home model promoted by the Institute of Medicine [65]; the principles proposed by Battersby and colleagues were organized within the framework of the chronic care model developed by Wagner and colleagues [66]. The Joint Principles of the Patient-Centered Medical Home, formulated and endorsed by the AAFP, the AAP, the ACP, and the AOA in 2007, and integrating behavioral care in 2014, are summarized in Table 21.4 [65, 68]:

To be feasible, the rewards for implementing the PCMH must exceed the cost of change: the AAFP, the AAP, and the ACP considered a three-component fee consisting of (1) an initial fee for service or visit, (2) a monthly management fee for practices providing medical home services, and (3) an additional bonus for reporting quality performance goals [65].

Effectiveness of the Patient-Centered Medical Home

Evaluations of several patient-centered medical home models have confirmed earlier findings about improved outcomes and satisfaction; patients report very positive experiences with patient centeredness, including being treated with courtesy and respect and communication with providers in a way that could be easy to understand [69]. The PCMH results in improvements in process measures, reduction in errors, and higher levels of satisfaction when patients identify with a medical home, but the evidence about its effects on clinical and economic outcomes is still scarce [70, 71].

The Patient-Centered Medical Home and Diabetes

Transforming the approach to patients with diabetes starts with the model of health care [72]. Despite the uncertainty about the effectiveness of the patient-centered medical home, identifying and overcoming barriers to achieve glycemic targets will become more important, not only to prevent diabetes complications but also to ensure reimbursement for diabetes management. In this scenario, the role of patients will also change; they will become "health care consumers" as health systems shift toward a model of value-based care, paramount of the patient-centered medical home [72]. Table 21.5 shows the effectiveness of interventions to implement the patient-centered medical home in diabetes management [73–87]:

Evidence about the effectiveness of the PCMH in diabetes management from meta-analysis and systematic reviews is even more limited. Ackroyd and Wexler selected and described the most effective interventions for diabetes care identified in a meta-analysis of 48 cluster randomized trials and 94 patient-level randomized trials attempting to determine the effect of individual quality improvement strategies for diabetes [88–91]. Albeit the studied strategies were not embedded in PCMH models, they provided some effect about the magnitude of the benefits expected on A1c levels [88]. The study showed larger effects at higher HbA1c base-

Table 21.5 The patient-centered medical home in diabetes management

Author(s), year and reference	Intervention	Size	Results
Kinmonth et al. 1998 [73]	Randomized controlled trial Routine care vs. routine care plus additional training	41 practices, 21 in the intervention group (250 patients), 20 in the comparison group (360 patients)	Better communication with doctors, greater treatment satisfaction and wellbeing in the intervention group
	One-year analysis, including practice effects and self-reporting by patients including communication with practitioners, satisfaction with treatment, style of care, and lifestyle		Nonsignificant differences in lifestyle and glycemic control
Steiner et al. 2008 [74]	Observational study: Community health networks organized and coordinated by physicians, hospitals, health departments, and social services	1200 primary care practices	Patients with A1c <7.0%: 47%
		750,000 patients	Patients with A1c >9.0%: 21%
		Each patient linked to a medical home	Blood pressure control ≥140/90 mmHg: 34%
		In addition to the Medicaid fee, a management fee to guarantee ongoing comprehensive primary care, 24-h on-call coverage and arrangements with other health professionals	Blood pressure control <130/80 mmHg: 37%
			LDL control ≥130 mg/dL: 19%
			LDL control <100 mg/dL: 5%
			Moderate reduction of unnecessary emergency department and specialty care
			No effect on costs
Paulus et al. 2008 [75]	Observational study Effectiveness of an innovation strategy for care model redesign	55 clinical practices	Goals achieved: Patients with HbA1c <7.0%: 34.8%
		450 physicians	Patients with HbA1c >9.0%: 21%
		20,000 patients with diabetes from a community of	Blood pressure control <130/80 mmHg: 43.9%
		2.5 million people poorer, older, and sicker than national benchmarks	Patients satisfying all nine quality indicators: 6.5%
		Components:	Low applicability
		Clinical leadership, Innovation team	
		Electronic record for ambulatory services	
		Financial alignment of incentives	

Table 21.5 (continued)

Author(s), year and reference	Intervention	Size	Results
Reid et al. 2010 [76]	Observational study	One prototype and two control clinics	Patients in the medical home reported better care experiences on six scales at 12 and 24 months
	Assessment of ambulatory care experiences and chronic illness care	6187 adults	Quality composite aggregate measures for 22 indicators, including diabetes, showed significant improvements within 2 years
		Quality measures included	Significant lower rates of staff burnout, emergency department visits, and hospitalizations
		HbA1c testing, HbA1c >9.0%, retinal examination, LDL-C screening, LDL-C <100 mg/dL, nephropathy monitoring	
Nutting et al. 2011 [77]	Observational study	36 small independent family practices selected to become PCMH and randomized into two groups: "facilitated" and "self-directed" intervention	Adoption of more components of the PCMH when using practice coaches
	Demonstration of the PCMH through a model with eight domains: access to care and information, practice services, care management, continuity of care, practice-based teams, quality and safety, health information technology and practice management		A composite score including HbA1c, blood pressure, lipoproteins, and retinal examination showed improvements in both groups
			Two years was not enough to implement the entire model and to transform work process
			Implementing discrete model components is easier than modifying existing roles and work patterns
Calman et al. 2013 [78]	Observational study	4595 patients with diabetes, including a subsample of 545 patients with HbA1c improvement	The transition to a PCMH increased number of encounters with outreach, diabetes education, and psychosocial services
	Changes in patterns of healthcare use throughout a 9-year period of practice transformation including recognition of centers at level 3 PCMH practices		All patients had visits with a primary care physician
			Annual levels of HbA1c decreased steadily during the 9-year period:
			Patients with A1c ≤9.0% showed increases of outreach services from 59% to 95.3%, diabetes education from 0.0% to 53.3%, psychosocial care from 9.0% to 27.4%, and small reductions in primary care from 99.7% to 99.4%
			Patients with HbA1c ≥9.0% showed increases of outreach services from 60.2% to 98.5%, diabetes education from 0.0% to 77.8%, psychosocial care from 11.2% to 35.3%, and primary care from 99.4% to 99.5%
			Patients with HbA1c ≥9.0% showed decreases from 10.72% to 8.34%

(continued)

Table 21.5 (continued)

Author(s), year and reference	Intervention	Size	Results
Slingerland et al. 2013 [79]	Cluster randomized clinical trial	13 hospital clusters, 506 patients with type 2 diabetes 237 randomized to patient centered, 269 to usual care	Patient-centered care was most effective and cost-effective in patients with baseline HbA1c >8.5%
	Effectiveness and cost-effectiveness of patient-centered care within specific HbA1c ranges	Primary outcomes: changes in HbA1c, quality-adjusted life years (QALYs), costs and incremental costs at 1 year	HbA1c reduction after 1 year: 0.83%, incremental cost-effectiveness ratio: $261.00 USD per QUALY
			Over a lifetime, 0.54 QALYs were gained at a cost of $3482.00 USD
			Care was not cost-effective at an HbA1c baseline level <7.0%
			Patient-centered care is more effective in patients with higher HbA1c levels
Pagán et al. 2013 [80]	Observational study	Analysis of the cardio-metabolic risk (CMR) data set including results of 19 simulated controlled trials for 100,000 individuals representative of the US population, comparing standard care to interventions targeting diabetes, obesity, and cardiovascular disease	The PCMH model has the potential to reduce the proportion of bilateral blindness, foot amputations, myocardial infarction, and death rate and is cost-effective ($7898.00 USD per quality-adjusted life)
	Long-term health and cost outcomes of implementing a PCMH model for adults with poorly controlled diabetes (A1c >9.0%) based on simulated data obtained from the Archimedes model of disease progression and health care		The PCMH model has potential long-term benefits to patients with poor diabetes control, health systems, and providers
Shah et al. 2015 [81]	Retrospective study	1038 patients, 713 from clinics with diabetes registries, and 325 from clinics without diabetes registries	Patients treated at clinics with diabetes registries did not have greater overall improvement in HbA1c levels than patients treated without diabetes registries in PCMH
	HbA1c values for patients from clinics with established diabetes registries vs. patients from clinics without diabetes registries in patient-centered medical homes		Additional research is needed to determine if diabetes registries are effective tools for the PCMH
Page et al. 2015 [82]	Observational study	10,000 patients treated by a centralized team of nurses and patient navigators who reach out to patients with scheduled appointments, motivational reminders and focus on patient encouragement, identification of barriers to keep appointments and communicate patient feedback to care teams	Ten of 11 measures of adherence improved from baseline to 12 months post-implementation, a 23.6% increase
	Effectiveness of the PCMH on improving access, quality of care, and adherence in patients with diabetes		Significant improvements in the number of patients receiving recommended care
			Centralized care coordination is effective for improving care in poor and underserved populations

Table 21.5 (continued)

Author(s), year and reference	Intervention	Size	Results
An 2016 [83]	Observational study	3334 adult patients with diabetes identified in the Medical Expenditure Panel Survey	11.4% of patients were classified in the PCMH group at baseline and only 3.6% remained in the PCMH for 2 years
	Associations between PCMH and process measures of diabetes care and adherence to oral antidiabetics (OADs)	Patients in the PCMH group vs. patients without PCMH features	Only 26.9% of the patients met all the diabetes care process measures, with a higher proportion in the PCMH (33.8%) vs. the non-PCMH group (26.0%)
		Process measures of diabetes care included ≥2 A1c tests, ≥1 cholesterol tests, foot examination, dilated eye examination, and flu vaccination at 1-year follow-up	No differences in the weighted mean MPR in the two groups
		Medication possession rate (MPR) was calculated for patients receiving OADs	Overall adherence rate: 47.7%
			Patients receiving PCMH had improvements in process measures of diabetes care, but not in adherence to OADs
Williams et al. 2016 [84]	Relationship between patient-centered care (PCC), diabetes self-care, glycemic control, and quality of life (QOL) in adults with type 2 diabetes	615 patients from 2 primary care clinics	PCC was significantly associated with physical and mental QOL, medication adherence, general diet, specific diet, blood sugar testing and foot care, but not in glycemic control
			Changes in clinical outcomes such as glycemic control need to expand throughout healthcare systems
Ratner et al. 2017 [85]	Relationship between patient-centered care (PCC), empowerment, and modification adherence in type 2 diabetes	Cross-sectional survey	PCC was significantly associated with medication adherence and diabetes empowerment
		166 patients completing a survey	
Brorsson et al. 2019 [83]	Effectiveness of a person-centered communication and reflection education model (GSD-Y) on young people with type 1 diabetes	Randomized controlled trial	Nonsignificant differences in glycemic control at 6 and 12 months in females and males, except for males at 12 months
		71 adolescents with type 1 diabetes starting continuous subcutaneous insulin infusion (CSII) and their parents	
		37 in the intervention group attending 7 group training sessions over 5 months using the GSD-Y model	
		34 patients in the control group received standard care	
Solberg et al. 2020 [84]	Effectiveness of practice systems primary care practices certified as medical homes on diabetes outcomes	Cross-sectional, observational study	92% of participating practices had data on diabetes care measures
		416 adult primary care practices completing questionnaires about the presence of medical home practice systems and 6 standardized measures of diabetes care including access, registry, coordination of care, care plans, and quality improvement	Practices certified as medical homes were more likely to meet a composite measure of optimal diabetes care

line and found that in addition to clinician education, patient education facilitated relay of information, electronic patient registries, and patient reminders, which are three major components of the PCMH: (1) team changes, (2) case management, and (3) promotion of self-management had significant effects reducing A1c levels [88]. Regarding non-glycemic outcomes, these strategies were associated with increases in aspirin use, the use of antihypertensives, lower levels of blood pressure, and LDL cholesterol [88]. Two systematic reviews and an integrative review addressed analyzed the effectiveness of the PCMH on diabetes outcomes [90–92]. In the study of Morgan and colleagues, each PCMH principle reached the following results:

Principle 1 (personal physician): a minimum of two visits to the same physician over 3 years and continuity of care result in lower HbA1c levels.

Principle 2 (physician-directed medical practice): nurse care managers and pharmacist care significantly reduce HbA1c levels compared to controls.

Principle 3 (whole person orientation): achieves significant reductions of HbA1c compared to controls.

Principle 4 (coordinated and integrated care): (a) two studies using technology enhancements to supplement care coordination showed reductions of HbA1c from a baseline of 7.35%; two smaller studies had no impact on HbA1c; (b) two studies providing cognitive behavioral therapy did not reduce HbA1c; (c) integration of nurse case managers reduced HbA1c by 2.0% from a baseline level of 10.0%.

Principle 5 (quality and safety): five studies assessing self-monitoring of blood glucose showed no reductions in HbA1c.

Principle 6 (enhanced access): (a) increased frequency of visits (every 2 weeks) achieved fastest control of HBA1c; (b) each 10% increase in missed appointments increase the odds of poor HbA1c control.

Principle 7 (payment): additional payments to physicians reduce HbA1c levels by 0.55% over 9 years.

The authors conclude that applying the PCMH in diabetes management improves glycemic control, and principles 2 and 3 are the most influential [90]. By comparison, albeit the systematic review by McManus and colleagues reported positive clinical outcomes, decreased use, and cost savings with the PCMH, it also recognized inconsistencies in the methods selected to study PCMH variables and the need to incorporate standardized instruments, reliable and valid, and measurements for PCMH research [91]. Finally, the review of 22 eligible studies by Olesen and colleagues demonstrated that the application of person-centered approaches is largely successful and superior to didactic diabetes self-management education to achieve outcomes, including psychosocial improvements and glycemic control [92].

Conclusion

Patient-centered care entered the health policy lexicon until 2001, when it was featured as one of the six aims to improve the quality of health care by the Institute of Medicine in the United States [59]. The IOM described patient-centered care as care that "is respectful to individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions [59]." The central role of the PCMH emerges from the growing body of data demonstrating that systems of care based on a strong foundation of primary care outperform systems of care based on specialty practices [61]. Patient-centered care is not simply capitulating to patients' requests nor it is "throwing information at people and leaving them on their own" [60]. Recent advocacy for the patient-centered medical home has arisen worldwide interest, and countless organizations have proposed steps to achieve such type of care, albeit many still do not understand the meaning of patient-centered care or are unwilling to accept it and even less implement it. The patient-centered medical home has become a worldwide initiative to reform health care and has advanced from pediatrics to involve internal medicine, geriatrics, palliative care, and collaborative disease management in diabetes, cancer, HIV infection, and patients with complex healthcare needs. Achieving a 2020 vision of patient-centered care will require champions among primary care leaders, employers, insurers, and politicians [64]. Patient-centered care matters because it is "the right thing to do," regardless of its contribution to achieve other goals, such as improved quality, patient well-being, or fair distribution of resources [93]. From the perspective of medical ethics, patient-centered care fulfills the obligation of healthcare professionals to place the interests of patients above else and to respect their personal autonomy [93]. Leading institutions in the advance of quality of health care such as Virginia Mason Medical Center in Seattle and Planetree, a nonprofit organization devoted to implement a comprehensive, patient-centered model of care with associates in America, Europe, Africa, and Australia, have successfully linked this approach to quality improvement and patient safety and satisfaction [93, 94]. In personalized care, patients and physicians work in collaboration to use the available evidence to select between a series of diagnostic and therapeutic options [95]. Shared decision-making recognizes the influence of patients' preferences and cultural values on clinical decisions; it is demanding and time-consuming and requires the integration of generalists and specialists, who may have competing interests [95]. Elevating patients' values, preferences, and needs over those of physicians or the healthcare organization is absolutely necessary [96]. Patient-centered and person-focused care are important but also different: in contrast with patient-centered care, person-focused care is based on the accumulated knowledge of people to improve recognition of

health problems and needs and facilitate the appropriate care for these needs with an specific focus on the whole person [96]. Patient satisfaction is an innovative approach. It has its roots in consumer marketing and is a measure of the capacity of products or services to meet or exceed the anticipated expectations of the customer [95]. The evidence of the effectiveness of the satisfaction-profit chain has stimulated the commercial use of monitoring and measurement of patient satisfaction; if accepted as a valid outcome, patient satisfaction should become and be held in the same standard as any other health intervention [95]. Patient satisfaction should be embraced as a desirable goal, but it must undergo a critical analysis [95]. After more than four decades and despite huge resistance to its principles from the advocates of fragmented, high-cost medical care, the patient-centered medical home is receiving worldwide acceptance, but at the same time, its strengths, weaknesses, opportunities, and threats have been recognized [97]. According to Rogers, its main strengths include (1) commitment to evidence-based medicine, (2) quality improvement, (3) the use of information technology, (4) application in routine medical care, and (5) understanding and facilitating the process of change. Its main weaknesses lie in the infrastructure including (1) the inability to provide universal provision of desired communication skills and shared decision-making, (2) the scarcity of health systems to document personal relationships between physicians and team members, and (3) the absence of formal care planning processes [97]. The PCMH is an opportunity for recognition, increasing compensation and reimbursement to individual physicians that will fund the development of infrastructure, and the perceived threats to family medicine involve programs emphasizing infrastructure, focusing on cost savings, the emergence of PCMH imposters, and the risk to deviate its focus in disregard that patient-physician relationships are at the core of the PCMH [97].

In 2013, the Institute of Medicine sponsored a workshop in which recommended the implementation of "strategies and policies at multiple levels to advance patients, in partnership with providers, as leaders and drivers of care delivery improvement through the protected use of clinical data, informed, shared decisions and value improvement," based on the premise that "prepared, engaged patients are a fundamental precursor to high-quality care, lower costs and better health [98]." The distinction between patient-centered care and better customer service lies in that it involves actions undertaken in collaboration with patients, not just on their behalf and requires clinicians to appropriately share power even when sharing feels uncomfortable [99]. According to Millenson, "prepared, engaged patients are the fundamental precursors to transform health care…patients and providers must change at the same time…a framework that enables a deeper partnership between patients and providers is more important than having "better patients" [99]." The momentum for widespread adoption of the PCMH has steadily built, and accumulating empirical evidence has shown that being attentive to the human experience improves quality, empowers patients, and improves health outcomes and engaging patients and family members as essential partners of the healthcare team has the potential to reduce costs [100]. Persisting barriers to widespread adoption are based on a relentless demand for solid evidence about the efficacy of the PCHM from traditional experts who are usually distanced and indifferent from patients and family experiences [100]. The future of the PCMH is still uncertain and involves several scenarios: from an increase in patient-centeredness as a function of current trends such as the Joint Principles of the Patient-Centered Medical Home to the extreme where health systems leave behind the PCHM from financial pressures pursuing lowering costs in acceptance of the negative consequences on the quality of health care [93]. To become a reality, the PCMH requires adopting new roles for patients and providers to achieve balanced levels of collaboration, positive activation, health literacy, and empowerment of patients and their families [101]. By putting patients—our customers—at the center in our practice, in our use of language and in our thoughts, the patient-centered medical home accomplishes one of the most legitimate aspects of medical practice and the most important outcomes for patients and their families: from "clinically relevant" to "patient or humanly important [102]." In a moving account of a dying man by Archie Cochrane, an act of brotherhood to another person is not medical, just human. Probably above science, this is what patients and their families expect and appreciate the most [103].

Multiple Choice Questions

1. Historically, the professional ideal of the physician-patient relationship is:
   (a) That patients have the most important role in making decisions
   (b) **That patients have a minimal role in making decisions**
   (c) That patients and physicians have equal roles in making decisions
   (d) That patients have very important roles in making decisions
   (e) That patient's relatives are most important in making decisions
2. The enhanced capacity to address patients' needs:
   (a) Is a waste of time
   (b) Increases the economic burden of health systems
   (c) Distracts physicians from their priorities
   (d) Has no effects on the outcomes
   (e) **Increases the efficiency and is also profitable**
3. Patient discrimination:

(a) Is unavoidable and necessary in some cases
(b) Reinforces the patient's compromise to adhere to therapy
(c) **Increases the use of diagnostic tests and services**
(d) Does not affect satisfaction with care
(e) Reduces the use of A1c measurements

4. The attributes of primary care include all of the following, except:
   (a) **Medical expertise**
   (b) Accessibility
   (c) Comprehensiveness
   (d) Longitudinal care
   (e) Coordination
5. A medical home was originally defined:
   (a) As the medical setting were patients are more comfortable
   (b) **As the repository of the medical record of children with chronic diseases**
   (c) As the patient's home with adaptations according to individual needs
   (d) As a "patient friendly" medical environment
   (e) As the place within clinical settings were physicians organize meetings
6. By comparison to disease management and specialized care, primary care:
   (a) Is less effective than specialized care
   (b) Is less professional
   (c) Is not supported by academic centers
   (d) **Is more effective to achieve better health outcomes**
   (e) Is exclusively empiric, not evidence-based
7. Clinical excellence involves all of the following, except:
   (a) **Expertise in the use of the most recent medications**
   (b) Promoting successful physician-patient relationships
   (c) Ability to find and apply information to solve clinical problems
   (d) Skillful negotiation within the healthcare system
   (e) Diagnostic acumen
8. In patients with diabetes, improvements in high-quality primary care result in significant reductions of:
   (a) A1c
   (b) Systolic and diastolic blood pressure
   (c) LDL-cholesterol and triglycerides
   (d) None of the above
   (e) **All of the above**
9. The principles of the patient-centered medical home:
   (a) Increase the costs of medical care
   (b) **Reduce HbA1c levels**
   (c) Increase physician burnout at unmanageable levels
   (d) Achieve nonsignificant reductions in HbA1c levels
   (e) Increases the use of diagnostic tests
10. The strengths of the patient-centered medical home include:
    (a) Commitment to evidence-based medicine
    (b) Quality improvement
    (c) Information technology
    (d) **All of the above**
    (e) None of the above

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Outpatient Diabetes Management and the Chronic Care Model

22

Joel Rodriguez-Saldana

Introduction

In the 1960s, diabetes was considered a common disease, even when it was much less common than today. The average practitioner treated 15 or 16 patients and hospital clinics admitted approximately 1000 patients each year [1, 2]. The first diabetes clinics were established in North America and Europe in the years following the discovery of insulin with the main objective of teaching patients the technique and principles of its use; only in Britain, 500 had been established from 1924 to 1973, even in isolated geographical locations [1, 3]. Hospital surveys showed that diabetes was controlled by diet and insulin, and early diabetic complications and patient education were overlooked by physicians, and involvement of nurses and dietitians was considered ineffective [4]. Successful clinics were the ones that had the vision, ability, and resources to institute comprehensive diabetic services coordinating activities of physicians, nurses, and dietitians to deliver multidisciplinary outpatient care, specialties (foot, eye, pregnancy, children, and adolescents), and diabetes education as essential components of their services [4–7]. These types of programs showed marked improvements in all areas of diabetes care, including diagnosis, assessment, hypoglycemia prevention, diet, and referrals [4]. In most of the hospitals, patients with diabetes admitted to hospitals were seen mostly by specialists, but the sharp rise in the prevalence of type 2 diabetes made this unpractical [8]. Hospital diabetes programs including telephone support for patients, screening by nurses, and a mixture of outpatient and inpatient services showed reductions in emergency room visits, decreases in the incidence of acute complications (ketoacidosis, hypoglycemia) and amputations, lower rates of broken appointments and complaints, and higher levels of patient and professional satisfaction [9, 10]. Most of the other hospitals told a different story: once referred, patients were supposed to be treated for life, doomed to take time out of work, and travel and wait to be seen by a different physician at almost every visit at the diabetes clinic. This approach of fleeting consultations was—and still is—unrewarding from every perspective [1]. Even when the estimated incidence of diabetes was 1.2–1.3% in England, diabetic clinics had such a large load that they became unable to devote sufficient time to difficult cases; medical manpower to deal with the growing workload was (and currently more than ever) met with increasing use of junior staff, resulting in large dropout rates, lack of adherence, high levels of patient dissatisfaction, and abysmal levels of quality of care [1, 2]. Taking into account that the average diabetic required seven to ten clinical visits every year, hospital demands meant establishing huge diabetic clinics with dissatisfaction and depersonalization for patients and staff [1]. In Germany and other countries, diabetes management was paternalistic; patients were admitted to stabilize blood glucose, and the lack of self-care support had negative consequences: glycosuria was preferred to prevent hypoglycemia, routine therapy consisted in one or two daily injections of medium-acting insulin, self-monitoring and changes in insulin dosage were not allowed, and education had degraded to "obedience training" to follow rigid dietary prescriptions consisting of six to seven meals with fixed amounts of carbohydrates, proteins and fats, and prohibition of sugar [11]. This approach was never assessed, but acute and late complications were frequent [11]. Hospital wards overflowed, resulting in patients treated in hallways, untimely access to appropriate medical advice, hospital resources largely devoted to episodic care for acutely and severely ill patients, low supervision by specialists, and high rates of acute complications [8, 9]. In-patient hospital care represented >80% of the direct costs of diabetes and was devoted to manage cardiovascular complications and renal disease [12]. At the same time, understaffing and low resources to outpatient facilities were associated with an excess in hospital admissions and direct costs [13]. With the increasing rates of diabetes occurring in recent decades, the number of patients admitted to hospitals continues to rise, with higher probabilities to die in the hospital, to occupy more bed days, and to incur in higher

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costs than people without diabetes [14]. The aim of diabetes care should be enabling patients to lead normal lives, with good metabolic control and free from complications. For many patients across the world, such an ideal is still far away [13].

Lessons Learned and Lessons Still Unlearned

Cumbersome clinics developed into adequate appointment systems and excessive waiting times and continuity was hampered by a multiplicity of doctors with limited experience and adequate supervision [15]. Failure of clinics established at hospitals, which rapidly became overwhelmed, obliged to increase the role of primary care physicians in diabetes management. General became aware of the importance of tailoring management to the patient's lifestyle, their expectation to be actively involved in their treatment, and their unwillingness to continue accepting medical advice without questioning [8]. General physicians from the United Kingdom were among the first to see that they could manage many aspects of diabetes in their own practice [2, 15–22]. Albeit the pace to provide ambulatory diabetes care was initially slow, many innovative schemes were described and initiated [23]. Combination of need and opportunity prompted the creation of "small clinics (mini-clinics) of general practice" where groups of general physicians were organized to assist groups of 80 to 100 patients to stop the flow of patient to hospital-based clinics devoted to difficult cases [2, 19–24]. Pioneering reports from Malins, Wilkes, Thorn, Russell, Hill, Singh, and colleagues showed that:

1. Diabetes could be looked after by family doctors [1].
2. General practice seemed the proper place to look after many diabetics, allowing general practitioners to become increasingly competent in diabetes care, to develop new expertise, able to contribute and notice that patients are willing to accept their professional competence [2–16].
3. Patients welcome being treated by general physicians; apart from attending close to their homes, they are glad to come into an atmosphere which is familiar and to be greeted by staff whom they know and that their personal and social circumstances are taken into account [16].
4. Coordinating and sharing "the diabetic workload" with hospital clinics raised community awareness about diabetes, allowing family physicians to deal with problems for which they were trained [18].
5. Diabetes care delivered by organized general physicians achieved similar levels of metabolic control to the ones reached in hospital clinics [19].

To summarize, increases in the number of patients with type 2 diabetes, longer life expectancy, and sophistication of treatment produced overcrowding and inadequacies of delivery in hospital-based diabetes care [25, 26]. Home and Walford reflected that "though some activities required expertise and resources only available in hospitals, most of them did not require them, as long as general physicians had access to blood glucose monitoring, dietetic, chiropody and nurse educational services" [25]. The need to reappraise the role of diabetes clinics was recognized by Thorn and Russell since 1973, but it was also essential to increase the access to effective diabetes management, because only a small proportion of patients attended hospital and outpatient clinics [25, 26]. Since 1985, it was acknowledged that the huge amount of people with diabetes in the community made it unrealistic to treat them in specialist outpatient clinics [26]. On the same year, Ling and colleagues proposed an analogy between traditional diabetes clinics and dinosaurs [27]:

> "Theories abound to explain the extinction of dinosaurs…perhaps they became too big to maintain efficient life…to adapt to the changing circumstances of the environment…or were unable to cope with all that was demanded to them. Whatever the reasons, perhaps the diabetic clinic could meet a similar fate." [27]

Four decades ago, ample evidence about the disadvantages, lack of efficiency, and high cost of specialist diabetes clinics had been documented, by comparison with the success of outpatient clinics in the United Kingdom, Germany, New Zealand, and the United States. Despite these observations, many other countries still breed and proudly maintain their "diabetes dinosaurs."

Transforming Diabetes Care

Surveys at facilities demonstrated (and continue to show) large discrepancies with recommended national and international guidelines [28]. A survey carried out by the Medical Advisory Committee (MAC) in Britain showed a scarcity of diabetes clinics or even examination rooms, resulting in lack of referrals; a variety of deficiencies in access to professional services, including obstetricians, ophthalmologists, dietitians, chiropodists, and nurses; a scarcity in the availability of resources to measure glucose and A1c; and absent or inadequate facilities to deliver diabetes education [29]. Nineteen recommendations were endorsed by the MAC, and a follow-up report 10 years later showed significant improvements in all the previously described deficiencies, albeit there was still room for improvement [30]. Even when resources were insufficient, reorganization and integration of services produced great improvements in healthcare standards. From its inception in the 1970s, the concept of diabetes centers evolved to a number of "different breeds in the 1990s, including depictions of structure and process" [15, 27, 31–33]. Dunn and colleagues identified four priority areas to be considered for implementation of the Diabetes Control and Complications Trial (DCCT) in Australia: (1) allocation and effective use of resources, (2) standards of care and quality assurance, (3) training and continuing education, and (4) research and evaluation [33].

Effectiveness of Diabetes Outpatient Management: The Evidence

The main objective of diabetes management became preventing or delaying the physical and social consequences of the disorder [26]. Early reports showed that transforming traditional to modern management methods was feasible, acceptable, and effective and produced significant improvements in A1c levels without higher risk of hypoglycemia [33]. Recent emphasis on cost-effectiveness came to realize that diabetes is a disorder that rarely warrants hospitalization; awareness to these facts reinforced the concept of diabetes ambulatory care [33]. Nevertheless and despite demonstrations of cost-effectiveness of ambulatory management, funding of ambulatory services remained (and continues to be) in huge disadvantage with hospital care [33]. The 1980s witnessed the emergence of multiple initiatives devoted to shift the focus of diabetes management from hospitals to outpatient clinics in Europe, North America, and Australia. Table 22.1 shows examples of outpatient diabetes programs manually collected or through a Pubmed search from 1971 to 2021 [19, 34–71]:

Table 22.1 Worldwide experiences about outpatient diabetes management

Year, country, and reference	Objectives	Type of study and intervention	Results
1984, UK [19]	Compare the degree of metabolic control achieved by mini-clinics with that achieved by a hospital clinic	Randomized controlled trial 57 patients receiving at mini-clinics 57 patients receiving treatment at hospital clinics	No significant differences were found between patients attending mini-clinics and those attending hospital clinics in blood glucose or HbA1c concentrations
1984 UK [34]	Compare routine care by a hospital diabetes clinic with routine care in general practice	Randomized controlled trial 97 patients treated at hospital clinic 103 patients treated by general practitioners	13.6% of patients in general practice were regularly reviewed and 4.8% had blood glucose measurement once a year All patients attending the hospital clinic were seen at least and had blood glucose measurements once a year HbA1c levels at the end of the study: General practice: 10.4% Hospital clinic: 9.5%
1988 United States [35]	Comparative effectiveness of community diabetes care and education on clinical outcomes	Prospective, randomized study 261 patients treated by 61 primary care physicians from 1980 to 1985 from four large and four small communities randomly selected Intervention: Four group sessions delivered by paramedical personnel Five-year follow-up	Significant changes in healthcare practices, including increasing use of multiple injections of insulin and self-monitoring of blood glucose Decrease in hospitalizations related to diabetes, probably representing changes in healthcare practices rather than changes in health status A1c levels unchanged
1988 Germany [36]	Efficacy of structured treatment and education on pharmacological therapy, A1c levels, triglycerides, and body weight	Prospective randomized study 114 patients with type 2 diabetes, 65 in the intervention group and 49 in the control group from five general practices Intervention: Preparatory course for physicians and assistants; four group monthly education sessions delivered by health professionals	A1c levels remained unchanged in the intervention group; significant decreases in triglycerides and weight loss Percentage of patients receiving sulfonylureas decreased from 68% to 38%
1993 Germany [37]	Feasibility and efficacy of structured treatment and teaching on routine primary health care	Observational study of a random sample of 17 physicians and their office staffs Remunerations to physicians and staff upon completion of a postgraduate training course 179 patients with type 2 diabetes Four 90- to 120-min sessions; groups of four to ten patients, partly based on the Grady memorial diabetes medical and education program [10] and previously participating in a controlled trial [36] program delivered by the office staff	Acceptance by physicians Significant decreases in A1c levels from 8.11% to 7.47%, body weight (mean 2.8 kg), use, and percentage of patients treated with oral antidiabetics

(continued)

Table 22.1 (continued)

Year, country, and reference	Objectives	Type of study and intervention	Results
1994 United States [38]	Follow-up of a structured treatment and education program on selection of pharmacological therapy, A1c levels, triglycerides, and body weight	Prospective, randomized study 440 patients with type 2 diabetes, 61 in the intervention group and 355 in the control group Ten-year follow-up 1981–1991	Positive changes in diabetes care and education Nonsignificant decreases in A1c and total cholesterol, significant increases in HDL cholesterol, significant decreases in hospital admissions, and small increases in percentage of patients receiving formal diabetes education Most of patients with type 2 diabetes managed on diet alone had never seen a dietitian Nonsignificant changes in ophthalmologic examinations Less patients managed with insulin
1997 United States [39]	Effectiveness and safety of intensive insulin therapy on outpatient, endocrine-based, multidisciplinary practice in patients with type 1 and type 2 diabetes	Longitudinal cohort study, 14 years duration 780 patients, 209 receiving long-term comprehensive treatment including cardiac screening with exercise treadmill tests, noninvasive thallium scan, and cardiology referrals if necessary 571 declined continuing care	Patients with prolonged exposure to comprehensive therapy had significant reductions in overall and cardiac mortality and lower incidence of renal failure Lower comorbidity scores associated with higher survival Two thirds of the patients declined receiving multidisciplinary, intensive care
1997 United States [40]	Compare the quality of ambulatory diabetes care delivered in a specialist clinic versus a general medicine clinic	Retrospective observational study; review of medical records 56 patients cared in the general medicine clinic 56 patients cared in the specialist clinic	Statistically significant differences in the percentage compliance in process of care criteria between the clinics including self-monitoring of blood glucose, foot and eye examination, and referral for diabetes education None of the records from either clinic achieved good quality of care criteria 52% of the general medicine clinic and 73% of the specialist clinic passed
1998 United Kingdom [41]	Changes in the percentage of patients receiving primary and secondary diabetes care over 5 years	Longitudinal study, 1990–1995 Seven general practices, five of them with organized diabetes programs	The proportion of patients treated in general practice doubled from 17% in 1990 to 35% in 1995 Patients treated in secondary practice fell from 35% in 1990 to 30% in 1995 Patients treated both in general and secondary practice fell from 6% to 2% Newly diagnosed and treated patients in general practice also increased Greater activity in primary care did not increase pressure on hospital services
1998 United Kingdom [42]	Effectiveness of training on a patient-centered intervention for general practitioners and nurses on outcomes	Randomized controlled trial 29 general practices receiving training about patient-centered care 252 type 2 diabetic patients 2-year duration	High initial levels of professional adoption by professionals Persistence after 2 years: 19% No significant biochemical or functional improvements
1998 United States [43]	Implementation of a diabetes improvement program in order to increase intermediate outcomes including retinal screening, foot inspection, risk-related education, testing for microalbuminuria and HbA1c and patient satisfaction	25 primary care clinics	Prevalence of HbA1c testing: 77% before the program; 80% afterwards changes in process measures before and after the program: Access to retinal screening: 66–86% Foot examination: 20–50% Smoking prevention and cessation: 14% to 10%

Table 22.1 (continued)

Year, country, and reference	Objectives	Type of study and intervention	Results
1999 Poland [44]	Effectiveness of a disease management program on A1c and fasting glucose, appropriateness of treatment modalities, and timing of therapeutic choices	Prospective study in outpatient clinics, 18-month duration Randomly selected patients: 88 with type 1 diabetes 132 with type 2 diabetes 177 pregnant women with type 1 diabetes, 81 received the structured program, 74 non-recipients 155 infants from women treated in these two groups	Patients with type 1 diabetes showed significant decreases in A1c, fasting and postprandial blood glucose, without severe hypoglycemia Nonsignificant body mass changes Patients with type 2 diabetes had significant decreases in A1c, fasting and postprandial blood glucose, without severe hypoglycemia, significant body mass decrease pregnant women not receiving the structured program had higher rates of hyperglycemia, preeclampsia, ketoacidosis, polyhydramnios and cesarean sections Recipients of the structured program showed higher APGAR scores in infants
2000 Israel [45]	Improving effectiveness of primary care providers to control glycemic levels	Retrospective cohort study of a 2-year national program conducted by a health maintenance organization based on continuing medical education, establishing guidelines and diabetes registries. One patient randomly selected for review from each of the physicians' diabetes registries	National response: 72.7%, 876 participating physicians Statistically significant improvements in performing all the monitoring parameters including weight: 35–60%, foot inspections: 40–63%, fundus examinations: 38.5–68.3%, HbA1c measurement: 38.5–68.3% Significant improvements in HbA1c: >9.0% decreased from 33.2% to 22.5%; HbA1c increased from 45.1% to 50.5%
2001 United States [46]	Effectiveness of a comprehensive diabetes management program including risk stratification and social marketing on clinical outcomes and patient satisfaction	Prospective trial, 12-month duration Two outpatient primary care clinics from a managed care organization 370 patients in the intervention group, 193 with available information at 12 months 623 patients in the control group	Significant improvements in glycemic control: Patients at low risk (A1c < 7.0%) increased by 51.1% Patients at moderate risk (A1c 7.0–8.0%) increased by 2.5% Patients at high risk (A1c ≥8.0%) decreased by 58.3% and 97.4% had changes in therapy Patients with blood pressure < 140/90 mmHg increased from 38.9% at baseline to 66.8%; 63.0% of patients with blood readings >130/85 mmHg at baseline had changes in medication Patients receiving lipid profile tests increased from 66% at baseline to 100% Patients with LDL >130 mg/dL decreased from 25.4% at baseline to 20.2% 76.7% of patients at the highest risk of nephropathy had a change in medications Patients receiving dilated eye examinations increased from 53.9% to 80.3% Foot examinations increased from 0 to 100.0%, 100% of patients and providers were satisfied with the program Patients in the control group remained unchanged

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Table 22.1 (continued)

Year, country, and reference	Objectives	Type of study and intervention	Results
2001 Denmark [47]	Effectiveness of a multifaceted intervention for general practitioners on 6-year mortality, morbidity, and risk factors of patients with type 2 diabetes	Open controlled trial randomization of practices to structured personal care or routine care 311 Danish practices, 474 general practitioners 243 in intervention group 231 in comparison group 459 patients randomized to structured care 415 patients randomized to routine care Regular follow-up and individualized goal setting supported by prompting of doctors, clinical guidelines, feedback, and continuing medical education	Equal rates of nonfatal outcomes and mortality in both groups Patients in the intervention group showed significantly lower fasting plasma glucose, HbA1c levels, systolic blood pressure, and total cholesterol levels More frequent use of metformin, doctors arranged more follow-up visits, referred fewer patients to hospital clinics and set more optimistic, individualized goals, education, and surveillance in primary care for at least 6 years, bringing risk factors of type 2 diabetes to a level to reduce diabetic complications without weight gain
2001 Netherlands [48]	Comparative effectiveness of a disease management to a shared diabetes care model	Observational non-randomized trial In the traditional care model, patients were seen by endocrinologists In the disease management model, patients were seen by nurse specialists, organized, and coordinated with specialists and health professionals in general practice 22 general physicians accepted the shared care model; 29 endocrinologists continued using the traditional model 74 patients agreed to participate in the shared care model; 47 patients continued using the traditional model	No differences were found between groups in quality of life, knowledge of diabetes, patient satisfaction, or consultation with caregivers Glycemic control improved in patients receiving shared care and deteriorated in patients receiving traditional care Factors influencing implementation of the shared care model: project management, commitment, power, and structure
2001 United States [49]	To evaluate the impact of primary care group visits based on the chronic care model on diabetes process and outcomes	Randomized controlled trial 57 primary care practices with at least 20 patients with diabetes per clinic 14 clinics were randomized to establish the chronic care model 21 clinics were randomized to deliver usual care 707 patients ≥30 years old randomly selected from an automated diabetes registry who completed baseline and follow-up information Intervention group: Periodic day chronic care clinics for groups of eight patients	At 24 months and compared with control patients, the intervention group received significantly more recommended preventive procedures and diabetes education; general health and bed disability days were significantly better, along with fewer specialty and emergency room visits Identical HbA1c levels in both groups
2002 United States [50]	Effectiveness of community-based diabetes care and a diabetes electronic management system (DEMS)	Observational study Three primary care practice sites Implementation of planned care and DEMS with 16 primary care providers	Improvements with planned care in A1c, cholesterol, microalbuminuria, tobacco advice DEMS associated with improvements in all indicators including microalbuminuria, retinal examination, foot examinations, and self-management support Organization and delivery of healthcare services improve documentation of clinical practice, adherence to performance measures and metabolic outcomes

Table 22.1 (continued)

Year, country, and reference	Objectives	Type of study and intervention	Results
2003 United States [51]	Effectiveness of diabetes care delivered by nurses and supervised by a diabetologist to meet the American Diabetes Association process and outcome measures versus usual care	Randomized observational trial 504 patients from two county clinics: 252 receiving nurse-directed diabetes care 252 patients receiving usual care as controls	Patients under nurse-directed diabetes care received almost all process measures significantly more frequently than control patients A1c levels fell 3.5% by comparison to a 1.5% decrease in patients under usual care After 1 year under nurse-directed care, A1c levels decreased to 7.1% and the median value fell from 8.3% to 6.6%
2003 United Kingdom [52]	Effectiveness of specialist diabetes clinics receiving patients from primary and secondary care	Observational prospective study, 2-year duration 19 specialist clinics 2415 patients referred to 19 specialist diabetes clinics led by GPs with special interest in diabetes, to alleviate increasing waiting times for secondary care Training: 2-day workshops for GPs, follow-up workshops and case reviews Multidisciplinary support from specialist nurses, podiatrists, dietitians, and retinal screening cameras	Significant increases in patient attendance Significant reductions in hospital attendance Main benefits: geographical accessibility, availability in community setting, short waiting times at most clinics and continuity of staff Reservations: lack of strategic planning in the location of clinics, long waiting times in some of them, poor communication for referrals Advantages: convenience to patients, acceptability, increased capacity of physicians
2004 United States [53]	Effectiveness of community-based, nurse case management and peer education to improve diabetes care, patient knowledge and satisfaction, reduce adverse beliefs in undeserved patients	Prospective study, 1-year duration 153 patients from six community clinics 76 non-randomized patients from the same clinics with A1c values ≥9.0% as controls	Patients in the intervention group: significant improvements in A1c, total cholesterol, LDL cholesterol, and diastolic blood pressure Nonsignificant changes among patients in the control group
2004 France [54]	Effectiveness of a local adaptation of a structured program on primary care to encourage intensive treatment of diabetes as routine practice	Prospective, randomized, controlled trial in a suburban and semirural area, 12-month follow-up allocation of all general physicians from a suburban and semirural area, 35 in the intervention group, 32 in the control group 192 patients in the intervention group 148 patients in the control group Three-day training and follow-up of physicians in the intervention group	Patients in the intervention group: more adequate management according to guidelines and referrals Significant decreases in A1c in the intervention group (0.86%) No significant differences in other clinical outcomes, incremental costs from the intervention No significant changes in quality of life
2008 South Africa [55]	Effectiveness of a nurse-led protocol and education-based system on diabetes management in a rural setting	Prospective non-comparative intervention 326 patients, 96% with type 2 diabetes Two rural nurses received 12-month training from a diabetes specialist One weekly hospital diabetes clinic, 14 monthly peripheral diabetes clinics Cornerstones: Patient education, drug dose titration, clinical outcomes	High levels of acceptance by patients and staff 980 patients enrolled within 9 months Significant decreases in A1c from 11.1 ± 4.2% to 8.7 ± 2.6% at 6 months Patients with baseline A1c >10.0% showed a mean 5.8% fall Diabetes education associated with significant A1c improvements Rates of hypoglycemia did not increase
2008 United States [56]	Effectiveness of a multicomponent organizational intervention in diabetes care and outcomes in primary care	Controlled clinical trial Components of the intervention: Electronic diabetes registry Visit reminders Patient-specific physician alerts	Over 24 months, 69,965 visits from 8405 adult patients with type 2 diabetes treated by 238 healthcare providers were recorded Significant net improvements in diabetes process measures in the intervention group including foot examination (35.0%), annual eye examination (25.9%), renal testing (28.5%), HbA1c testing (8.1%), blood pressure monitoring (3.5%), LDL testing (8.6%) Mean HbA1c levels and comorbidities decreased significantly and intervention practices had significant greater improvements to achieve HbA1c, systolic blood pressure, and LDL goals

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Table 22.1 (continued)

Year, country, and reference	Objectives	Type of study and intervention	Results
2008 Australia [57]	Compare clinical outcomes of patients attending diabetes clinics with different models of care	Diabetes centers participating in a national diabetes information audit were invited to nominate if they provided (A) routine diabetes care only, (B) routine care and structured annual complications screening, (C) annual review and complications screening in a shared-care system with specialized diabetes clinic	Analysis of 3052 patients from 18 diabetes centers showed that patients receiving management under models B and C had higher rates of attainment of HbA1c and blood pressure targets and higher rates of nephropathy and lipid screening
2010 United States [58]	Effectiveness of systems-based care in an undeserved population to reduce disparities in care for cultural, ethnic, commercial, and socioeconomic minorities	Implementation of disease registry and management system in four community health centers from a suburban practice network	Community health center patients meeting guidelines showed significant improvements in clinical outcomes except percentage of patients with A1c >9.0% Statistically significant discrepancies persisted between community health clinics and suburban practices in percentage of patients with A1c <7.0%, LDL <100, retinopathy, and microalbuminuria screening Community health centers lagged in all comparisons
2010 United States [59]	Comparative effectiveness of nurse-directed diabetes management between a nonintegrated model in which patients were removed from primary care clinics and followed by supervision from endocrinologists versus an integrated model in which patients were seen by nurses under supervision of primary care physicians	Observational study, 9–12 months 387 patients randomly assigned to the nonintegrated model 178 patients referred to the integrated model	25% of patients in the nonintegrated model used insulin (mostly bedtime), 75% of patients in the integrated model used intensified insulin regimes A1c decreased 1.9% in the nonintegrated model and 3.9% in the integrated model in the integrated model: 90% of patients met blood pressure goals, 96% met LDL goals, and 47% met all three goals of treatment (A1c, blood pressure, LDL)
2010 Mexico [60]	Effectiveness of structured diabetes management on the quality of primary diabetes care	Seven-year statewide diabetes program Training, feedback, and reminders to general physicians, nurses and health professionals to implement 43 outpatient multidisciplinary diabetes clinics at urban and rural health centers Organizational arrangements to reduce waiting times, avoid rotation of staff and increase time for baseline and follow-up visits Statewide diabetes registry	4393 patients with type 2 diabetes After five visits, significant increases in the percentage of process indicators were documented in the diabetes registry, including body mass index, blood pressure, A1c, total cholesterol, and foot examination Outcome measures showed significant decreases in A1c and fasting blood glucose Nonsignificant changes in systolic/diastolic blood pressure and lipoprotein levels
2011 Netherlands [61]	Effectiveness of structured diabetes care from the perspective of patients and healthcare professionals in routine practice	Quasi-experimental study, 4 years duration Comparison of structured care (SC) and usual care (UC) SC including organizational components: Multidisciplinary cooperation, clear task division, and cooperation between general practitioners, diabetes specialist nurse, and dietitians UC based on clinical guidelines performed by GPs, nurses, or assistants Questionnaires sent to healthcare professionals and patients in the SC and the UC group	No differences between SC and UC in yearly and three monthly checks More patients in the SC group received diabetes education by diabetes specialist nurses All practices in the SC used the diabetes registry GPs in the SC were significantly more satisfied than GPs in the UC group More patients in the SC group reported contact with GPs, nurses, assistant and dietitians, received adequate education about diet and foot care, and knew their blood glucose level One year after SC finished, the effects of structured care were still visible

Table 22.1 (continued)

Year, country, and reference	Objectives	Type of study and intervention	Results
2013 Denmark [62]	Follow-up of study referenced as [47]	Observational study 1381 patients aged ≥40 years and newly diagnosed with type 2 diabetes from national registries 19-year follow-up	Group differences in risk factors from the 6-year follow-up had leveled Lower rates of microalbuminuria and triglycerides in the intervention group Similar rates in all-cause mortality between the intervention and control group Prompting, feedback, clinical guidelines, continuing medical education, individualization of goal setting, and drug treatment among patients with newly diagnosed type 2 diabetes lowers the risk of complications
2013 United Kingdom [63]	Effectiveness of integrated, structured primary diabetes care in partnership with specialists to challenge the secondary care status quo and to shift resources within the health economy	Consistent messages tailored and delivered to primary and secondary care providers to persuade them about the need and benefits of change Two phases of implementation: establishment of community diabetes teams Changing the secondary care model, establishment of six "super-clinics": Pregnancy, renal dialysis, insulin pumps, acute type 1 diabetes, type 1 education, adolescents	Significant improvements of care; 85% of patients discharged from secondary care; estimated savings: £59,940.00 per year 108 patients receiving appropriate treatment in the "super-six" clinic 2996 patients received DESMOND education training 287 clinicians received training Consistently positive relationships with clinicians and staff Patient feedback overwhelmingly positive
2013 Australia [64]	Effectiveness of an integrated primary/specialist model for community care for complex type 2 diabetes management compared with outcomes for usual care at a tertiary care hospital for diabetes outpatients	Prospective open controlled trial in a primary and tertiary care setting 330 patients with type 2 diabetes ≥18 years allocated to community-based care by general practitioner with advanced skills and endocrinologist partnership or to usual care in hospital diabetes outpatient clinic	By comparison to the usual care group, patients in the intervention group showed a 0.8% decrease in A1c; 21% to 42% achieving an HbA1c target of >7.0%, significant improvements in blood pressure and total cholesterol, and significantly higher combined A1c, blood pressure and LDL cholesterol targets Community-based, integrated models of complex diabetes care delivered by general practitioners with advanced skills, produce clinical and process benefits compared with tertiary diabetes outpatient clinics
2015 United States [65]	Comparative effectiveness of in-clinic health coaching by medical assistants on diabetes and cardiovascular risk factor control versus usual care	Randomized controlled trial 441 patients from two primary care clinics Health coaching delivered by three medical assistants who received 40 hours of training and were embedded as part of the care team Patients randomized to usual care had access to any resources available at the clinics except for health coaching Primary outcome: Composite measure of HbA1c, systolic blood pressure and LDL cholesterol Secondary outcome: Meeting all three goals	Participants in the coaching arm were more likely to achieve goals for one or more uncontrolled conditions at baseline and more likely to achieve control of all conditions Almost twice of people in the health coaching group achieved the HbA1c goal and more likely to achieve LDL cholesterol goals Nonsignificant changes in systolic blood pressure Health coaching by medical assistants has the potential to alleviate nationwide deficiencies in diabetes control in an environment of deepening primary care clinician shortage

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Table 22.1 (continued)

Year, country, and reference	Objectives	Type of study and intervention	Results
2015 Australia [66]	Effectiveness of an integrated model of care for patients with complex type 2 diabetes on potentially preventable hospitalizations	Prospective controlled trial, 36 months duration multidisciplinary, community-based, integrated primary-secondary diabetes care compared to usual care at a hospital diabetes outpatient clinic 327 patients, 206 of them hospitalized	Compared with the usual care group, patients in the integrated model of care group were nearly half less likely to be hospitalized for a potentially preventable diabetes-related diagnosis after 24 months models reduce hospitalizations
2016 United States [67]	Association between patient-centered care (PCC), diabetes self-care, glycemic control, and quality of life (QOL)	Two adult primary care clinics 615 patients	PCC was significantly associated with QOL, medication adherence, general diet, specific diet, blood sugar testing, and foot care, but not with glycemic control Increasing patient-centered care is required for changes in outcomes occur
2017 United Kingdom [68]	Comparative effectiveness of enhanced diabetes primary care with more expensive integrated specialist-community diabetes services	Eight primary care practices and eight matching neighboring practices Enhanced practices had primary care physicians and nurses with an interest in diabetes who attended monthly diabetes education meetings and provided care plans and audits Control practices provided integrated primary-specialist care services	No significant differences were noted between enhanced and primary specialist services Enhanced primary diabetes care has similar outcomes to that provided by more expensive primary-specialist care
2017 Brazil [69]	Effectiveness of a structured intervention to improve type 2 diabetes management in primary care in a defined region	Comparative observational study 230,448 patients, 124,779 in the intervention group 105,669 in the control group 61 family strategy team professionals (FHS) from 2 cities 29 in the intervention group 32 in the control group One awareness raising workshop with heads of municipal health departments of the selected cities, with extensive participation of FHS health professionals Local management teams, reorganization, and local action plans to improve diabetes care Three training sessions for FHS professionals	Significant but negative differences in staffing the intervention group, including physicians and nurses By comparison with the intervention group, control group had better outcomes including multidisciplinary management, adherence to treatment, diagnostic tests, and educational activities The intervention had no detectable impact despite an enormous investment in money and manpower
2019 Denmark [70]	Comparative assessment of type 2 diabetes management shared between a specialized outpatient clinic and primary health care	Randomized, controlled, noninferiority study 140 patients with type 2 diabetes assigned to quarterly checkups by general practitioners (GPs) for the shared care group or to be treated by endocrinologists for the control group	Twelve months afterward, HbA1c increased 0.2% in the shared care group and 0.1% in the control group. Noninferiority was confirmed in the per protocol and intention to treat analysis
2019 United States [71]	Effectiveness of an interdisciplinary diabetes team model to improve glucose control in a primary care rural setting	An interdisciplinary diabetes team was established in a family rural medicine clinic Patients were referred if their HbA1c was ≥9.0% for initial consultation and follow-up visits	Ninety-four patients attended a baseline and at least one follow-up visit within 6 months. Significant reductions in HbA1c from 10.25% to 8.7% between baseline and follow-up visits were observed; 86% of patients had lower HbA1c levels at follow-up, and in 33%, it was <8.0%

Outpatient Management of Type 1 Diabetes

Traditional models for type 1 diabetes are organized around specialists in pediatric diabetes centers of excellence involving multidisciplinary team to deal with education, nutrition, and psychosocial adjustment [72–74]. A limited number of patients with type 1 diabetes are treated by primary physicians, but even in developed countries, availability and geographical distribution of specialists are real obstacles to refer all these patients to diabetologists [73, 74]. Even in the United States, it was estimated that in 2014, the shortage of adult and pediatric endocrinologists was of 1500 and 100, respectively, and that the gap for adult endocrinologists would continue to increase [75–78]. Models of primary care for type 1 diabetes are scarce, but innovative strategies have been conceived and implemented. Based on experiences collected as one of the participating centers in the DCCT, in 1988, the International Diabetes Center organized a team comprising three family physicians, four endocrinologists, a clinical epidemiologist, three nurse specialists, and a dietitian and developed Staged Diabetes Management (SDM), a systematic approach to support clinical decision-making including clinical pathways or DecisionPaths to start, adjust, maintain, or change therapies [72, 79]. The experience with SDM in the United States demonstrated its feasibility, its capacity to standardize clinical practice, reduce clinical inertia, and establish criteria for referral [79]. International dissemination of Staged Diabetes Management has confirmed its feasibility and effectiveness [44, 54, 59].

Comorbidity and Multi-morbidity in Diabetes Management

Treating a chronic disease like diabetes is often complicated by the coexistence with multiple medical conditions and by social and psychological deterrents. Currently, the most common chronic condition among adults is multi-morbidity [80, 81], in the words of Kate Lorig, "the Disease of the 21st Century" [82]. The contribution of multi-morbidity to the global burden of disease is already huge, but projections are of great concern: it is estimated that during the last 15 years of life, one-half of the newborns in industrialized countries will suffer multi-morbidity and its consequences, including poor quality of life, psychological distress, worsening functional capacity, longer hospital stays, higher costs of care, and higher mortality [83–88]. MM also affects processes of care resulting in complex self-care needs; multiple organizational problems; polypharmacy; increased use of emergency facilities; difficulties to apply clinical guidelines; fragmented, costly, and ineffective care; and higher mortality rates [83–92]. Multi-morbidity is important for diabetes management because besides its long-time recognized association with metabolic and cardiovascular risk factors, the frequency of non-diabetes-related (or non-apparently related) comorbidities is high and frequently influential in diabetes management. Negative outcomes associated with multi-morbidity partly result from the fact that healthcare delivery traditionally has been conceived and designed for patients with "isolated" diseases [83]. Fortin and colleagues state that "clinical practice is still based on a single disease paradigm which is not appropriate for patients with complex and overlapping health problems [84]". To make matters worse, most clinical trials exclude patients with comorbidities, limiting generalization of research results [92]. Diabetes management clearly applies to these statements: until recently, clinical guidelines failed to recognize the importance of comorbidity, and it has been demonstrated that this is a limiting factor to their implementation [83]. Research about the epidemiology of multi-morbidity, its consequences, and its effects on the process of care is still very limited [92–96].

Multi-morbidity (MM) was originally defined by Feinstein in 1970 as "coexistence of two or more diseases, pathological conditions or clinical entities in the same patient" [97], while comorbidity (CM) is defined as the presence of one index disease and at least one another chronic condition in the same person [98]. Due to the growing ambiguity around the use of both terms, van den Akker and colleagues suggested that CM be defined according to Feinstein's original definition and MM be defined as "the co-occurrence of multiple chronic or acute diseases and medical conditions," and in 2010 Boyd and Fortin provided a simpler definition of MM as "the coexistence of two or more chronic conditions, where one is not necessarily more central than the others" [99].

MM and CM have become great challenges and additional pressures on healthcare systems. They represent an additional burden on the acute care model which impedes in many cases, even recognizing the main complaint in a hurried visit. Healthcare interventions have successfully delayed death by managing (not curing) diseases but have also led to a marked increase in the coexistence of separate diseases in individuals [100]. In less than three decades, the frequency of chronic diseases and associated patterns of comorbidity and multi-morbidity has escalated for several reasons: (1) lowered diagnostic thresholds, (2) new diagnoses, and (3) true increases of some diseases, such as diabetes [100, 101].

Comorbidity and Multi-morbidity in Diabetes

Comorbidity and multi-morbidity are extremely frequent among patients with diabetes; its association with cardiovascular risk factors has been recognized for a long time, but coexisting conditions in other categories are also frequent and influential in diabetes care and outcomes. From

this perspective, Piette and Kerr proposed a framework to consider ways by which associated chronic conditions could influence diabetes medical care, self-management, and outcomes [102]. They classified comorbidities in three groups: (1) clinical dominant conditions, (2) concordant versus discordant chronic conditions, and (3) symptomatic versus asymptomatic chronic conditions, and recognized the preeminence of diseases like cancer, end-stage renal failure or severe cognitive impairment in the realities of diabetes care and life expectancy. Comorbidities in the second group are common and compete for time in the medical visit, for economic resources and support from patients and their families; some of them are inextricably related to the outcomes of diabetes care (hypertension, dyslipidemia), and others are related to mental health (depression, stress) or to recently explained pathogenic mechanisms (diabetic cheiroarthropathy). The third group includes chronic conditions which should be managed regardless of symptoms, worsening, or recurrence [109]. Most reports about diabetes and chronic disease are about associations with single medical disorders or clusters of chronic conditions, in denial of the unifying role of diabetes in the pathogenesis of apparently disparate disorders in the cardiovascular, musculoskeletal, or digestive systems. Table 22.2 depicts reports about comorbidity in patients with diabetes:

Linking Multi-morbidity in Diabetes

The results of studies described in Table 22.2 confirm the increasing prevalence of comorbidity and multi-morbidity in persons with diabetes and its negative effect on quality of care, quality of life, and direct costs. The prevalence more than doubles the observed rates in people without diabetes, partly explained by the long-time recognized aggregation of cardiovascular risk factors. The concept of multi-morbidity started from a unidimensional approach, the simple counting of co-occurring diseases in which patients are usually managed for each individual disease according to specific guidelines, and by different physicians [119, 120]. The logical limitations of this approach have encouraged a shift to integrated approaches to meet the needs of individual patients [120]. The current view and classification of human diseases dates to the late nineteenth century and derived from the observational correlation between pathological analysis and clinical syndromes [121]. Over the years, attention to the interactions of multiple, apparently unrelated diseases occurring at different levels led to a vertical dimension which attempts to clarify the complex interactions of multi-morbidity at the cellular, organizational, community, and even the emotional levels [122]. Aron addressed the additional burden imposed by multi-morbidity on diabetes self-management, the conflicts, and potential risks of glycemic control [119]. A new, holistic view suggests that common linked pathophysiological pathways underlie the development of diseases in a non-organ-specific manner and that multiple diseases within one person, regardless of symptoms or organ-system, are not necessarily caused by independent mechanisms [120]. Considering the highly internal organization of the cell, it would be possible to improve the one-gene-one-disease approach by developing a conceptual framework to link all genetic disorders with the complete list of disease genes, resulting in a global view of the "diseasome," the combined set of all known disease/gene associations [123]. In the "human disease network," nodes represent diseases, and two diseases are connected if they share at least one gene in which mutations are associated with both diseases [122]. Coexistence of intricate molecular links between subcellular components and disease genes raises the possibility that diseases may not be as independent of each other as physicians traditionally think and that diseases form networks in which two of them are connected if they share at least one gene [122]. Diabetes management at the one-gene-one disease level ignores its complexity, clearly illustrated by the aggregation of concordant and discordant conditions. From this perspective, clinicians should move forward and start thinking in multiple dimensions! [119].

Comorbidity in Clinical Practice

Several instruments have been devised to measure comorbidity [124], but the most widely used at the outpatient level is the Charlson Co-morbidity Index (CCI) [125]. Developed by Mary E. Charlson and colleagues, the CCI assigns weights from 1 to 10 for a variety of diseases, including diabetes without organ damage [126]. Summing the weights of each condition, the relative 1-year mortality risk is calculated: six diseases have weights of 2, one disease has a weight of 3, and two diseases have weights of 6; scores range from 0 to 10, although higher scores are possible for severely ill patients [126]. The CCI has been used to estimate the prognosis of comorbidities in a variety of disciplines, from dermatology to oncology, and its power to predict morbidity, mortality, costs, and hospitalizations has been validated and compared with other measures [127]. Its use continues to extend, and it has become available in several versions of online calculators.

Comorbidity is usually managed by different specialists ("as many as necessary"), using independent clinical guidelines. This approach is ineffective and conflicting, increases the demand of professional services and costs, and may even pose risks for the patients. Current disease-oriented guidelines do not account the interactions between different diseases and are designed to manage single chronic conditions [128]. Innovative approaches have been proposed to address the challenge of comorbidity, such as the Adriane principles, a tool to support decision-making during consultations in primary care that involve patients [129, 130]. The Adriane principles were designed to foster an innovative concept in

Table 22.2 Comorbidity in patients with diabetes

Year, author, and reference	Country	Patients	Prevalence of MM and comments
Kerr et al. (2007) [103]	United States	1901 diabetes patients responding to a survey	40% of patients had at least one microvascular comorbidity, 79% had at least one macrovascular comorbidity, 61% had at least one nondiabetes comorbidity including arthritis (55%), cancer (14%), lung disease (10%) Patients with greater number of comorbidities placed lower priority to diabetes and had worse diabetes self-management scores Type and severity of comorbid conditions, beyond the comorbidity count, influence diabetes self-management Patients with comorbidities need additional support to accomplish self-management activities
Ose et al. (2009) [104]	Germany	3546 patients with type 2 diabetes	The number of comorbidities and the interaction between management and comorbidities have a significant impact on quality of life Structured diabetes management may help to counteract the negative effect of comorbidity
Zhang et al. (2010) [105]	Australia	17,095 patients with diabetes ≥65 years	80% of patients had four or more comorbid conditions Only 1% had no comorbidities 18.7% were receiving medications for chronic obstructive pulmonary disease or asthma 17.5% were receiving nonsteroidal anti-inflammatory drugs 7.1% had cancer 4.4% were receiving medications for dementia Patients with comorbidity have low utilization of preventive diabetes services Competing health demands and patients' preferences are very influential in diabetes care
Wermeling et al. (2012) [106]	Netherlands	2086 well-controlled patients with type 2 diabetes, including A1c, systolic blood pressure, and total cholesterol	Compared to patients without comorbidities, patients with type 2 diabetes, and comorbidities had much lower health status despite good diabetes control Physical limitations and functional impairment are decisive Physicians have to take into account patients' health status and integrate the impact of comorbidities into diabetes care

(continued)

Table 22.2 (continued)

Year, author, and reference	Country	Patients	Prevalence of MM and comments
Luijks et al. (2012) [107]	Netherlands	Prospective observational study 712 adults with newly diagnosed type 2 diabetes during a 17.3-year observational period from a practice-based research network	Prevalence of "any type" of comorbidity: 84.6% 70.6% had one or more discordant comorbid disorders, mostly musculoskeletal and mental, chronic functional somatic symptoms, or deafness 27.2% had three or more comorbid diseases At the date of diabetes diagnosis, patients had between 1.5 and 2.1 comorbidity clusters Diabetes management in general practice is complex in terms of chronic comorbidity "Straightforward" patients without comorbidities are extremely rare" Diabetes management demands management of comorbidities, including discordant diseases Validity of clinical guidelines is questionable if they do not consider comorbidity A patient-centered approach can be of added value
Pentakota et al. (2012) [108]	United States	42,826 patients with new-onset diabetes	Prevalence of comorbidity: 80% Prevalence of discordant illnesses: 30.1% Prevalence of both concordant and discordant illnesses: 25.5% Prevalence of concordant illness: 13% Prevalence of a dominant illness different to diabetes: 12% Comorbidity from concordant illnesses is associated with increased visit frequency and higher likelihood to receive recommended diabetes care Patients with discordant illnesses received less diabetes care and patients with dominant illnesses received markedly lower diabetes care
Teljeur et al. (2013) [109]	Ireland	424 patients with type 2 diabetes treated in general practice	Prevalence of comorbidity: 90% 25% of the patients had ≥4 additional chronic conditions, the most common: Hypertension: 66% Heart disease: 25% Arthritis: 16% Comorbidity significantly increased the number of medical visits and polypharmacy The variety of conditions emphasizes the complexity of diabetes management and the importance of maintaining a generalist and multidisciplinary approach
Alonso-Morán et al. (2015) [110]	Spain	126,889 patients with type 2 diabetes	87.6% of men and 92% of women with type 2 diabetes had at least another chronic condition 1.7% of men and 1.9% of women with type 2 diabetes had 10 or more chronic conditions; by comparison, 54.2% of men and 57% of women without diabetes had at least another chronic condition Ten morbidity clusters were identified, the most common related to cardiovascular risk factors and heart disease Patients with diabetes are at higher risk of peripheral vascular disease, heart failure, hypertension, and chronic renal disease

Table 22.2 (continued)

Year, author, and reference	Country	Patients	Prevalence of MM and comments
Ricci-Cabello et al. (2015) [111]	England	Cross-sectional study of 54,220,050 patients from 7884 family practices	Prevalence of diabetes concordant conditions: Hypertension: 13.8% Obesity: 11.25% Chronic kidney disease: 4.16% Coronary heart disease: 3.34% Stroke and TIA: 1.66% Atrial fibrillation: 1.45% Heart failure: 0.71% Prevalence of diabetes-discordant conditions: Asthma: 5.95% Depression: 5.78% Hypothyroidism: 3.17% Cancer: 1.87% Chronic obstructive pulmonary disease: 1.79% Severe mental disorders: 0.87% Epilepsy: 0.78% Dementia: 0.55% Concordant conditions were positively associated with quality of diabetes care Epilepsy and mental health disorders were negatively associated with quality of diabetes care
Adriaanse et al. (2016) [112]	Netherlands	Cross-sectional study of 1676 patients with type 2 diabetes Quality of life was measured and comorbidities were recorded from self-reports	21.5% of patients reported no comorbidities Diabetic patients with comorbidities showed lower scores in quality of life than patients without diabetes Comorbidities reducing most significantly quality of life included retinopathy, heart disease, peripheral artery disease, lung disease, incontinence, back, neck and shoulder disorders, osteoarthritis, and rheumatoid arthritis
Sancho-Mestre et al. (2016) [113]	Spain	491,854 patients with diabetes identified and selected through clinical codes	70% of patients suffered from more than two comorbidities, the most common: Hypertension: 68.4% Dyslipidemia: 53.3% Mental disorders: 25.0% Osteoarticular disease: 24.5% Cardiovascular disease: 14.4% Pharmaceutical expenditures increased according to the number of comorbidities
Bralic Lang et al. (2017) [114]	Croatia	10,264 patients from 449 primary care practices	Prevalence of comorbidities: 77.7%; the most common: Cardiovascular: 69.7% Endocrine and metabolic: 30.1% Musculoskeletal: 14.0% As the number of comorbidities increase, patients were less likely to achieve glycemic control Despite limited time, general physicians are able to deliver proper treatment of patients with type 2 diabetes and comorbidities Comorbidity increases clinical inertia and treatment fragmentation by physicians, institutions, and therapies

(continued)

Table 22.2 (continued)

Year, author, and reference	Country	Patients	Prevalence of MM and comments
Petrosyan et al. (2017) [115]	Canada	861,354 adults with diabetes Compliance with three quality measures according with type of comorbidity	Prevalence of comorbidity: 86% Diabetes-concordant conditions: 20.7% Diabetes discordant: 15.6% Patients with diabetes concordant and diabetes discordant conditions: 49.8% Receipt of all recommended monitoring tests in diabetes is higher in patients with diabetes concordant and discordant conditions (30.2%) and lower in patients with diabetes discordant conditions (19.6%) Hospitalization for diabetes complications is lower in patients with concordant conditions Meeting goals for HbA1c does not prevent hospitalizations for diabetes, especially in patients with comorbidities Other factors, including self-monitoring of blood glucose, glycemic control, lifestyle changes, patient education, and drug therapy are more important
Pouplier et al. (2018) [116]	Objectives: 1. Quantify development and composition of multi-morbidity (MM) following the diagnosis of type 2 diabetes 2. Effectiveness of structured personal diabetes care between patients with and without MM	Randomized controlled trial: 19 years follow-up of 1381 patients with newly diagnosed type 2 diabetes receiving structured personal diabetes care or routine diabetes care	MM increased from 31.6% at diagnosis to 80.4% at 16 years Cardiovascular and gastrointestinal diseases decreased; musculoskeletal, eye and neurological diseases increased
An et al. (2019) [117]	Association between different types of comorbidities and quality of diabetes care, quality of life, and total healthcare expenditures	Retrospective observational study from a sample of 8292 patients with diabetes from a medical expenditure survey Twenty chronic conditions identified and classified as (1) diabetes only, (2) diabetes plus concordant comorbidities, (3) diabetes plus non-concordant comorbidities	Prevalence by categories: Diabetes only: 11.4% Concordant comorbidities: 40.5% Discordant comorbidities: 48.1% Patients with diabetes and comorbidities received better quality of diabetes care Patients with discordant comorbidities had lower quality of life and higher health care expenditures
Pati et al. (2020) [118]	Impact of comorbidities on quality of life of receiving primary care	Cross-sectional study: 942 patients with type 2 diabetes assessed with a questionnaire for measuring comorbidities, physical and mental health scores, sociodemographic and clinical variables	Comorbidity was statistically associated with lower scores of physical and mental health Lower quality of life increased with the number of comorbidities Clinical relevant scores occurred with peptic disease, chronic lung disease, visual impairment, depression and stroke, duration of diabetes, insulin use, and obesity

medical decision-making for patients with multi-morbidity in primary care by establishing realistic goals at the center, and three core principles: (1) individualized management, (2) prioritization of patients' preferences, and (3) interactive assessment [129, 130].

Multi-morbidity in Diabetes Management

Comorbidity or multi-morbidity has negative effects on mental status and quality of life and increases the frequency of medical visits and the risk of death [87, 131]. Integrated, simplified care of comorbidities involving physical diseases and mental disorders can decrease disabilities and is associated with significant reductions in total healthcare costs and hospital costs [89, 94]. The challenge to deliver patient-centered care for people with comorbidities is to provide the right care for the right person at the right time, but current medical structures do not support multidimensional care and encourage treating only disease-specific outcomes [132]. The number and type of comorbid diseases have multiple consequences in patients with diabetes, create competing demands, and promote clinical inertia [133, 134], impairs controlling diabetes and cardiovascular risk factors [135,

136], and increases use and costs of antidiabetics and all other classes of medications [137]. For patients with diabetes, dominant comorbidities including end-stage diseases, severely symptomatic conditions, and acute health problems determine prognosis and dictate everyday experiences [138]. Shared decision-making and comorbidity hierarchies are critical to guiding treatment decisions in patients with diabetes [138]. Diabetes guidelines typically focus on decreasing microvascular and cardiovascular complications in disregard of the burden of comorbidity [138]. The current narrow focus on single diseases should be replaced with a holistic view and approach to established patterns of comorbidity and multi-morbidity [139, 140]. Only a radical rethinking of health systems will facilitate the transition and challenges multi-morbidity and its associated disability [141].

Diabetes and the Chronic Care Model

Well-trained, hard-working clinicians frequently unable to deliver effective services or achieve diabetes goals [142]. Usual medical care often fails to meet the needs of patients with chronic diseases; meeting their complex needs is the single greatest challenge facing organized medical practice, usual care is still not doing the job, and the medical system is perfectly designed to achieve the mediocre results it achieves [142–144]. Many patients with diabetes have no access to medical care or receive inadequate treatment [145]. New paradigms have been proposed for improving care for patients with chronic diseases in the face of the ineffectiveness of usual care, and the evidence about the benefits of innovations in ambulatory care has encouraged new paradigms. Based on clinical experience, literature reviews, and suggestions of an advisory panel, Wagner and colleagues developed a model to improve chronic illness care by incorporating successful interventions [146]. The Chronic Care Model (CCM) is based on the reality that in chronic diseases, the outcomes are largely dependent on the efforts, resources, and support of patients and their families [146]. Successful treatment requires that patients are well informed about their disease, the place where they can receive treatment, and to have greater control over their treatment [147]. The CCM is not a quick and easy fix or an abstract theory; it is a multidimensional solution to a complex problem, a concrete guide to improve clinical practice [145]. Care for chronic noncommunicable diseases (NCDs) is a global problem; the CCM is a tool to deliver integrated management for NCDs in primary care and a practical guidance for healthcare program managers, policy-makers, and stakeholders to plan and deliver high-quality services for people with NCDs [148].

The CCM assumes that medical care is centered in the interaction of patients and practice teams, with self-management support from the community and organization of health care inside and outside the health system [149]. By comparison to usual care, in which isolated physicians give orders to patients, chronic disease management involves collaboration with clinicians from diverse disciplines (nurse case managers, physicians, pharmacists, social workers, dietitians, lay health workers) who communicate regularly and participate in the care of a defined group of patients [149]. Interventions that improve care and outcomes fall into four categories: changes to the way care is delivered (practice redesign), changes to patient education and support (patient education), interventions to educate or remind providers (expert system), and changes to information systems (information) [142]. The "six pillars of the chronic care edifice" include (1) community resources and policies, (2) healthcare organizations, (3) self-management support, (4) delivery systems design, (5) decision support, and (6) clinical information systems [145, 150, 151]. Incorporating most or all its elements is associated with improved quality of care and outcomes in chronic disease management [152]. Interventions in the four categories improved care across different chronic conditions and resulted in the largest improvements in care and outcomes [142].

The CCM in Diabetes

In many ways, diabetes care is the prototype for the CCM and became an emblematic clinical scenario to assess its effectiveness; accumulating evidence shows that the CCM provides a framework for optimal diabetes care [152]. Table 22.3 summarizes two decades of interventions implementing the CCM for diabetes management since 2001:

- Diabetes represents an ideal clinical setting to implement the CCM. After two decades of being conceived however, the number of studies and, most importantly, the number of health organizations and national health systems who have implemented the CCM is still scarce. Beyond endorsement from international agencies [148] and with remarkable exceptions [162], most of the studies and interventions to implement the CCM have occurred in developed countries; adaptations to preexisting models are the rule, instead of studies devoted to implement the CCM "as it is" [164]. Most of the studies continue to appear in previous systematic reviews, not only because of their importance but also because of scarcity of new trials [165, 166]. Available studies show limitations, including non-blinding of participants, brief follow-up, the absence of self-report measures for behavior change, small sample size, inadequate training of health professionals, and the absence of registries and electronic medical records [166]. Despite these challenges, 24 years after publication of the description of the Chronic Care Model, a large amount of experience using the CCM has accumulated worldwide. More evidence about its effectiveness in diabetes management is essential.

Table 22.3 The Chronic Care Model (CCM) in diabetes management

Year, country, and reference	Design and intervention	Results	Comments
2001 United States [153]	Randomized controlled trial 57 primary care practices serving ≈500,000 people Patients with diabetes ≥30 years attending chronic care clinics at 3–6-month intervals. Components of the CCM: Baseline assessment Individual visits with primary care physicians, nurses, clinical pharmacists, one group peer support session	Patients receiving the intervention were more likely to receive preventive procedures, foot and retinal examinations, and medication reviews, without significant differences Significant higher participation rates in diabetes education Nonsignificant differences on physical function, depression measures, days confined in bed, and patient satisfaction Mean A1c levels equally high in both groups, cholesterol levels equally lower Chronic care clinic patients visited primary care more frequently; the increase was associated with significant reductions in specialty, emergency room visits, and hospital admissions	Redesign of care including delegation of roles within the practice team, involvement of other disciplines, organization of visits and follow-up and integration of psychoeducational interventions is important for success
2006 United States [154–156]	Multilevel, cluster design, randomized controlled trial 19 hospitals 166 primary care clinics 1400 academic physicians 90,000 patients with diabetes Stepped implementation of the six elements of the CCM Delivery of diabetes self-management (DSMT) training	The number of CCM recognized programs grew from 3 to 21 over 4 years Significant differences in HbA1c among patients receiving DSMT in hospital programs versus primary care 2–3 greater proportion of patients received SMDT at primary care offices versus patients referred to hospital-based programs	The CCM is an effective framework to support DSMT With reliable clinical information systems, educators can demonstrate the benefits of DSMT on HbA1c levels Improvements in program and patient outcomes can be sustained, financially self-supporting
2007 United States [157]	Controlled pre- and post-intervention study, 1-year duration 1170 patients with type 2 diabetes, 613 assigned to chronic care 557 assigned to usual care	Patients in both groups had improvements in HbA1c, blood pressure, and lipoprotein levels Participants in the intervention group had a 2.1% greater reduction in cardiovascular risk	Collaborative interventions using the CCM lower cardiovascular risk factors in patients with diabetes
2007 United States [158]	Observational study 30 small, independent primary care practices 90 clinicians, including 60 physicians, 17 nurses, 13 assistants who completed a questionnaire assessing the use of the CCM 886 patients with diabetes	Use of the CCM was significantly associated with lower HbA1c levels and ratios of total cholesterol to high-density lipoproteins Every unit increase in the use of the CCM was associated with a 30% A1c reduction and a 0.17% reduction in the lipid ratio	Clinicians in small independent primary care can incorporate elements of the CCM in their practice, with higher levels of process and intermediate outcomes of diabetes care
2009, 2010 Belgium [159, 160]	Four-year evaluation of a project based on the CCM Implementation based on the ACIC survey Implementation: First stage: 2300 patients with type 2 diabetes Follow-up: 4174 patients	Overall ACIC scores improved from 1.45 at baseline to 5.5 at the end of the study Significant improvements in HbA1c and total cholesterol in the intervention group Insufficient assessment of long-term complications Crucial steps for strengthening primary care: Local steering group, appointment of program managers, willingness of well trained and motivated care providers Barriers include complexity of the intervention, lack of quality data, inadequate information technology, lack of commitment, unsustainable funding	Adapting the CCM in primary diabetes care has opportunities and bottlenecks Further improvements are required to deliver the components of the CCM Albeit remarkable improvements were achieved, primary care providers lack opportunities and resources to take full responsibility for chronic care

Table 22.3 (continued)

Year, country, and reference	Design and intervention	Results	Comments
2010 United States [161]	Intervention trial 25 practices, 4 physicians per practice Implementation of the CCM measured through staff and clinical management surveys, chart audits and patient questionnaires	Low levels of implementation Sites with higher levels of CCM implementation showed improvements in diabetes assessment and treatment Physical activity counseling for persons with overweight and obesity was associated with CCM implementation, except for people with diabetes	Modest levels of CCM implementation Unsupported primary care is associated with improvements in diabetes care and higher rates of behavioral counseling
2015 Philippines [162]	Observational study Two primary healthcare units in semirural and rural municipalities Adaptation and implementation of the CCM Assessment of chronic illness care and glycemic control	Significant improvements in HbA1c, glycemic control, and chronic care scores	In resource-limited settings, the CCM improves the quality of primary diabetes care
2017 Italy [163]	Population-based study 8486 patients exposed to the CCM versus 8486 nonexposed patients Four-year duration	Significant improvements for adherence to clinical guidelines, lower risk of cardiovascular complications, protective effects against neurological, cardio-cerebrovascular complications and mortality	Implementation of the CCM improved diabetes management and reduced cardiovascular outcomes

Diabetes as a Complex Disease

Zimmerman, Lindberg, and Plsek described three kinds of problems in the world: simple, complicated, and complex [167]. Simple problems are clearly defined, with straightforward solutions. Complicated problems don't have straightforward solutions but can be dissected into groups of simple problems. Complex problems have multiple components, commonly not initially perceived and appear during the process of solution. To address complex problems, expertise is important but not sufficient, and uncertainty and risk are trademarks. Diabetes management is a complex task. Complexities of diabetic control were recognized five decades ago by Franklin Williams and colleagues, who described the degree in which a variety of continuing intervening factors, including (1) biological, (2) psychological, (3) appropriateness (and timeliness referring to clinical inertia) of medical recommendations, (4) adequacy of diabetes education (from a pedagogic to an andragogic approach in adults), (5) patient's resources (cognitive, socioeconomic, motivation, health literacy), and (6) family and social support, converge to achieve the lifetime challenge of day-to-day control [168]. Despite these arguments, reductionist approaches abound and prevail in diabetes management. Countless efforts have failed and continue to fail from denial of this reality. Recognition of complexities of diabetes care starts by identifying the three components of successful diabetes management: (1) patient activation, (2) self-care, and (3) support. Each one is essential to achieve the desired outcomes; all of them are directly related to the crucial role and responsibility of people with diabetes and their families. Self-care and support are associated with the capacity to deliver multidisciplinary, patient-centered care, including diabetes self-care education and support. The absence of any one of these components leads to clinical failure, waste of economic resources, and overall dissatisfaction from patients, their families, payers, and providers.

Conclusions

> "Establishing the best evidence is not the same as implementing the best practice, though the former does provide a basis for the latter"
> Philip Davies [169]

Randomized controlled trials, meta-analysis, and systematic reviews have confirmed that unstructured community care is associated with poorer follow-up, worse glycemic control, and greater mortality [166]. This is the case of health systems reluctant and resistant to change of the acute care approach in diabetes management like Mexico where three decades of ill-devised, unstructured, short-range, and low resource efforts have not been able to improve clinical outcomes or to reduce diabetes morbidity and mortality [170, 171]. By comparison, worldwide experiences accumulated in almost four decades confirmed the effectiveness of primary diabetes care to reduce risk factors, improve the process of care, decrease referrals to specialists, and direct costs when complex, multifaceted interventions and organizational interventions that facilitate structured and regular review of patients are established, in addition to patient education and with support [19, 34–70, 172, 173]. Essential components of structured diabetes management include (1)

targeting patients at high risk, intensive reducing A1c levels ≥9.0%, blood pressure ≥ 160/95 mmHg, and foot care in patients at high risk of foot ulcers [56, 174]; (2) establishing diabetes registries for data collection, reporting, support, and quality improvement [175–179]; (3) local physician champions with specific interest in diabetes and chronic care management and responsible to coordinate the implementation of the patient-centered medical home [56, 179]; (4) team management involving primary care providers, nurse practitioners, dietitians, and "physician extenders" [179–181]; and (5) health coaching to make sure that patients understand the care plan involving "knowing their numbers," shared decision-making, promoting behavior change, and medication adherence [181].

Controlled clinical trials have demonstrated that achieving the goals of metabolic control by lowering glucose, blood pressure, and LDL cholesterol reduces the risk of microvascular and macrovascular diabetes complications [182]. Nevertheless, most diabetic patients do not meet these recommended goals; prevailing and persistent structure and process deficiencies in primary care impede the achievement of outcomes. Studies of the level of diabetes care provided "in the real world" and especially in primary care continue to show that professional performance is suboptimal and conflicting with recommendations [145, 183]. Challenges in diabetes translation, starting with the urgency to change healthcare systems, were described by Anderson 30 years ago, but a large proportion of persons with diabetes worldwide continue to be treated "as usual" [184]. Establishing effective, sustainable, long-term outpatient diabetes management is one of the greatest challenges in this era.

Multiple Choice Questions

1. Initial experience of hospital diabetes clinics in Europe showed that:
   (a) It was absolutely feasible to treat all patients with diabetes.
   (b) Every patient could receive treatment from highly trained specialists.
   (c) Nurses and dietitians were not required.
   (d) Physicians were the most important elements of success.
   (e) **Clinics became overwhelmed, resulting in long waiting times and dissatisfaction.**
2. Successful clinics are the ones:
   (a) With the most qualified medical specialists
   (b) **The ones who had the vision and were able to offer comprehensive services**
   (c) Charging the highest fees for their services
   (d) In which patients could be admitted to a hospital
   (e) Having access to the newest medications
3. Diabetes management from a paternalistic approach:
   (a) Is essential to make patients follow physicians' orders
   (b) Has been shown to reduce the risk of acute complications
   (c) Reduces the risk of chronic complications
   (d) Has received high levels of satisfaction from patients and their families
   (e) **Has never been assessed and is associated with acute and late complications**
4. Planning of diabetes services:
   (a) **Needs to be broader beyond those available in most centers**
   (b) Requires procuring for new medications.
   (c) Must be based on the expertise of specialists.
   (d) Occurs exclusively at the medical office.
   (e) Is not important; patients may attend whenever they want.
5. Implementation of a model based on the DCCT in clinical practice requires all the following except:
   (a) Allocation and effective use of resources
   (b) Standards of care and quality assurance.
   (c) Training and continuing education.
   (d) Research and evaluation.
   (e) **Recognition that patients are unable to self-manage**.
6. Outpatient diabetes management:
   (a) Is feasible, acceptable, and effective
   (b) Produces significant improvements in A1c
   (c) Does not increase the frequency of hypoglycemia
   (d) Is not inferior to management in hospital clinics
   (e) **All of the above**
7. Comorbidity:
   (a) Should be treated by different specialists
   (b) Is very uncommon
   (c) Has no impact on diabetes management
   (d) **Is increasingly frequent, "the disease of the 20th Century"**
   (e) Are never be more important than diabetes
8. Compared with people without diabetes, the prevalence of comorbidity in patients with diabetes:
   (a) Is very rare
   (b) Is lower
   (c) Is equal
   (d) Is slightly higher
   (e) **Is more than double**
9. The Chronic Care Model:
   (a) **Recognizes that outcomes are largely dependent on patients and their families**
   (b) Depends on the availability of all the necessary medications
   (c) Recognizes the preeminence of physicians in all the decisions of management
   (d) Involves fragmentation of services

(e) Is important but very expensive and complicated

10. Diabetes management:
    (a) Is simple and straightforward
    (b) Is complex but outcomes are certain
    (c) **Is complex and outcomes are uncertain**
    (d) Depends exclusively on physicians' expertise
    (e) Is independent of patients' resources

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Clinical Practice Guidelines, Evidence-Based Medicine and Diabetes

23

Joel Rodriguez-Saldana

Organization and year	IDF 2017[a]	CDA 2018[b]	JOSLIN 2020[c]	AACE 2020[d]	NICE 2020[e]	ADA 2021[f]
HbA1c	<7.0%	<7.0%	<7.0%	≤6.5%[g]	<6.5% <7.0% for patients on drugs associated with hypoglycemia	<7.0%
Preprandial glucose	<110 mg/dL	70–120 mg/dL	80–130 mg/dL	NR	NR	80–130 mg/dL
Postprandial glucose	<180 mg/dL	90–180 mg/dL	<180 mg/dL	NR	NR	<180 mg/dL
Bedtime glucose	NR	NR	90–150 mg/dL	NR	NR	NR
Blood pressure	<130–140/80 mmHg	<130/80 mmHg	≤140/90 mmHg	<130/80 mmHg	<140/80 < 130/80 with kidney, eye, or cerebrovascular damage	<140/90 mmHg
LDL-C cholesterol		<77.3 mg/dL	<70 mg/dL for patients with ASCVD[g] <100 mg/dL for patients without ASCVD[g]	High risk: <100 mg/dL Very high risk: <70 mg/dL Extreme risk: <55 mg/dL	NR	<100 mg/dL
Triglycerides	NR	<132.8 mg/dL	≤150 mg/dL	<150 mg/dL		<150 mg/dL
HDL cholesterol	NR	NR	≥40 mg/dL	NR		>40 mg/dL in men >50 mg/dL in women
Non-HDL-C	NR	NR	NR	High risk: <130 mg/dL Very high risk: <100 mg/dL Extreme risk: <80 mg/dL	NR	

[a]International Diabetes Federation
[b]Canadian Diabetes Association
[c]Joslin Diabetes Center
[d]American Association of Clinical Endocrinology
[e]National Institute of Clinical Excellence
[f]American Diabetes Association
[g]ASCVD Atherosclerotic Cardiovascular Disease

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The Unwarranted Variation in Health Care and Its Consequences

In 1938, J. Alison Glover reported a remarkable finding: high variations in the rates of tonsillectomy in small areas of Britain in which the probability of undergoing the operation was 20 times higher in children living 7 miles apart [1]. Despite the amount of similar evidence collected for almost four decades, when John Wennberg published his first article on unwarranted variations in the delivery of health care in 1973, he was largely ignored [2]. Over the next four decades, Wennberg and his colleagues collected compelling research against the traditional view of quality of health care as "the best in the world" at the expense of high variability in costs. They showed that a large part of the medical services delivered in the United States and other countries was not only unnecessary, it also inflicted a large burden in costs and was potentially harmful [3]. Following these observations, in 1967, Wennberg and Gittelsohn developed a database to identify and compare the underuse of care among neighboring hospital service areas assuming that lack of access and undertreatment were the most important problems. Surprisingly, they found the opposite: large unjustified variations in the delivery of services among neighboring communities. Instead of under-service and undertreatment, large variations in the availability of resources and using services in neighboring communities without scientific basis were the rule [4, 5]. Wennberg came to the conclusion that medicine had wrapped itself in a mantle of science, but much of what doctors were doing was based more on hunches than good research [2]. These landmark studies were not warmly received: the first two reports had to be published in Science and Scientific American [6, 7], because journals with wide clinical readerships rejected them arguing that patient demand was the only explanation for variations in healthcare delivery, and those studies would be of no interest to the readers [5]. Despite the initial and persistent resistance to accept their existence, similar variations in hospital admissions, length of stay, and specific surgical procedures started to appear in other regions in the United States [8, 9]. Wennberg's studies led to healthcare reforms at the federal and state levels in the United States, but in most places in the world, these proposals are still unacceptable [2]. Despite continuing advances in medical science, regional variations in surgery have not decreased, rates of common surgical procedures remained stable, and it is very likely that comparable variations could be demonstrated for diagnostic and medical procedures [10–14]. Clinical inertia, personal beliefs, and economic interests are still relevant barriers to standardize medical practice. Instead of applying "evidence-based," "eminence-based medicine" prevails and rules. A patient's odds of undergoing surgical, diagnostic, and therapeutic procedures is more related to where he or she lives than on clinical decisions. "What you get depends on where you live and who you see [15]."

Substantial variations in diagnostic, medical, and surgical procedures are associated with (1) differences in health systems, (2) practice styles of physicians, and (3) characteristics and preferences of patients [16]. Beyond structural differences and recognizing the role of patients to pursuit and select health care, physicians' beliefs about the effectiveness of clinical interventions and their personal interpretation to what constitutes evidence are the main contributing factor. Patients in high-intensity areas, with high availability of services, do not experience better health outcomes [17]. The use of clinical practice guidelines (CPG) to apply scientific evidence has become increasingly important to address unexplained variations as an effort to standardize clinical practice and to improve the quality of health care.

The Ascent of Clinical Practice Guidelines

One of the most important factors influencing physicians is the use of clinical policies [18]. In 1989, Robert Brook announced the emergence of the movement leading to practice guidelines based on (1) documented high rates of unexplained variations, inappropriate care, adverse events, and medical errors; (2) escalating financial pressures and cost-containment; (3) the accelerated introduction of technology; and (4) unprecedented questioning and scrutiny of medical care [19–21]. All these issues demanded collecting clinical evidence about efficiency, cost-effectiveness, and the impact of medical interventions on quality of life [21]. Attention shifted to the development of methods with the ability to provide valid and reliable guidelines about the best interventions "for the real world," based on high standards of quality, understandable and practical evidence-based information, not simply anecdotal, consensus-based, opinionated, nihilistic, or with limited scope [22, 23].

Articles about guidelines started to appear in the 1960s, and the title "clinical guidelines" was mentioned since the 1970s, but 1990 became the landmark. Brooke was accurate in his prediction: the vision and efforts of a distinguished group of leaders, including David Eddy, Stephen H. Woolf, Scott Weingarten, Marilyn Field, and Kathleen Lohr in the United States; Richard Grol in the Netherlands; Jeremy Grimshaw, Ian Russell, and Martin Eccles in the United Kingdom; and the pioneering work of the Agency for Health Care Policy and Research (AHCPR), the Institute of Medicine (IOM), the American College of Physicians, the Veterans Health Administration in the United States, the National Institute of Clinical Excellence in England (NICE UK), and the Guidelines International Network (G-I-N) led to an explosion in the development of CPGs and created a worldwide discussion about their methodology, implementa-

tion, impact, and quality of health care [24–31]. They understood the required roles to improve organizations to attain its professional goals: to advance – from the craft stage in which skills are passed from practitioner to apprentice to a stage where experience is collected and systematized to establish principles of integrated structure of thought [24].

Critical pathways were first used in industry; the critical path method was developed in the 1950s to coordinate multiple contractors to identify the sequence and critical path that would drive the timeline of a project and started to be applied to health care in the 1970s to define the optimal sequencing and timing of interventions by physicians, nurses, and other staff for diagnostic or clinical procedures [25]. Critical pathways are devoted to (1) improve the health status of large amounts of individuals; (2) reduce unwarranted variations in patient care; (3) minimize delays and resource utilization; (4) enhance communication; (5) decrease costs; (6) reduce variations in outcomes; and (7) maximize the quality of health care [25, 26].

Defining Clinical Guidelines

Different definitions of CPG have been proposed. According to the AHCPR, CPG are "systematically developed statements developed to assist practitioners' and patients, decisions about health care to be provided for specific clinical circumstances [29]," the IOM defines CPG as "all the information relevant to approach the diagnostic and therapeutic management of a clinical problem [30]," and Margolis defined them as "all the relevant information to approach the diagnostic and therapeutic management of a clinical problem, logically driven by a clinical algorithm [32]. CPG evolved from pathways to direct the diagnosis or management of symptoms or signs to graphical descriptions of quality improvement. Their primary goals are (1) to improve the quality of care, enforcing professionalism, accountability, and efficiency as part of professional activities (2) to support systems in decision-making for clinicians and patients [33].

Rationale and Evolution

Clinical practice guidelines (CPG) became the preferred methods to influence medical decisions and to develop practice policies beyond the traditional approach in which practice policies evolved through collection of "standard and accepted" practices, which were not to be changed [34, 35]. The traditional approach had several issues, including (1) obligatory compliance with policies and norms and the expectative that people must perform them without deviation. In this approach, the former defines the latter and creates two problems: (1) it is not anchored on reality because policies are not explicitly described or analyzed; and (2) the outcomes are subjective [34]. Eddy proposed substituting global subjective judgment for an evidence-based approach, in which clinical decisions were supported by evidence. The steps that he described to design practice policies are still paradigms [34–39]:

1. Formulate the problem to be assessed by the guideline.
2. Identify and interpret the evidence.
3. Synthesize the evidence including magnitude of benefits and harms.
4. Direct comparison of benefits and risks.
5. Estimate costs.
6. Compare health outcomes and costs.
7. Setting priorities.
8. Design a practice policy.

CPG have to be flexible because outcomes must be assessed by heterogeneous audiences including providers, payers, and users [39]. The Clinical Practice Guideline movement consolidated through the common interest of leaders and institutions from the United States and Europe. Multiple approaches were published over one decade until the 28th Bethesda Conference analyzed their association with quality of care, development, and implementation [40–45].

Development of CPG

Clinicians need simple, patient-specific, user-friendly guidelines which include three basic components: (1) description of decisions to be made and their possible consequences; (2) collection of valid evidence to make informed decisions at key decision points; and (3) presentation of evidence and recommendations in a concise, accessible format [46]. The process starts with the pathway of CPG development [47] and the need to abandon the consensus approach, a method of subjective judgment in which participants "simply decide what to recommend" and privileges the biases of traditional, empirical, medical practice [48]. The consensus approach, evolved from collective personal experiences which are sanctioned by selected, frequently biased, groups of experts, without explicit criteria to select the evidence supporting specific recommendations, is open to misuse and reluctant to meet quality standards [21, 48–52]. Components of high-quality guidelines are summarized in Table 23.1 [31, 46–72]:

Challenges of Implementation

Despite the resources and expertise devoted in their development, serious deficiencies persist in the adoption of CPG

Table 23.1 Stages in the Development of Clinical Practice Guidelines [24, 30, 31, 46–72]

Stage	Description
1	Composition of guideline development group Identifying and refining the subject inviting clinicians, experts on the topic, patients, potential users, or evaluators Define the topic in precise terms including condition or disease, interventions, patient population, evidence, and outcomes
2	Cost analysis and hidden costs involved in implementation. Health interventions are not free, people are not infinitely rich, and budgets are limited. Costs of alternative preventive, diagnostic, and management strategies for each clinical situation
3	Target audience and clinical setting, objectives, and scope
4	Groups or individuals responsible to develop and implement the guideline
5	Establishing a panel of 10–20 members balancing scientific, practical and political concerns, including primary care professionals with specific interest, health authorities, medical specialists with expertise in the guideline topic, one epidemiologist, one health economist
6	Conflicts of interest: Disclosure of financial and nonfinancial conflicts of interest for members of the guideline development group
7	Decision-making process: The method to develop the guideline: (a) Informal consensus conference or working party (b) Formal consensus: Expert panel in compliance with appropriateness ratings (c) Evidence-based: Linked to the quality of scientific evidence (d) Explicit method based on the evidence-based approach (e) Synthetic method: Preparing a draft by one specialist and one general practitioner, review by the editorial panel, circulation for comments by local doctors to create a refined version for printing and implementation
8	The causal pathway of the guideline: An explicit method describing the use of evidence to establish effectiveness, outcomes, and adverse consequences of interventions
9	Defining questions to be answered to reach recommendations, types of evidence, and relevant information for analysis
10	Literature retrieval and review; using systematic review methods to identify and evaluate evidence related to the guideline topic
11	Trade-offs to balance benefits and harms of recommendations
12	Wording recommendations: Clarity and precision, use of direct, specific terms, clear and concise statements, in active voice Avoid using vague, nonspecific words and passive voice
13	Rating of evidence and recommendations based on established hierarchies by the Canadian Task Force of the Periodic Health Examination (CTF-PHE), the United States Agency for Health Care Policy and Research (AHCPR), or the United States Preventive Services Task Force (USPSTF)
14	Disclosure of uncertainties in recommendations and algorithms including lack of scientific evidence, expert opinion, special clinical circumstances
15	Addressing physicians' confidence in the correctness of guidelines, tailoring, or customization
16	A clear strategy of implementation including population to be benefited, reminders for physicians and patients, quality improvement strategies to reduce clinical and managerial discordances
17	Dissemination and learning, ascertainment that the guideline reaches the users who will learn from it and practice accordingly
18	Peer review and stakeholder consultation: Internal and external evaluation by experts, professional societies, government organizations, consumers, health management organizations, insurers, clinicians. Monitoring of intermediate and long-term clinical outcomes
19	Effects on quality of health: Number of patients receiving process measures, achieving outcome measures, cost-effectiveness, patient satisfaction
20	Regular review and updating or expiration
21	Feasibility and sustainability: Long-term likelihood to operate "in the real world"
22	Strategies to enhance implementation, identification of barriers; anticipative solutions, formats, and channels for dissemination, adaptation of educational resources
23	Financial support and sponsoring organization

resulting from perceived conflicts with clinical freedom; divisive, individualistic personalities; poor planning; lack of resources; and the absence of strategies to change practitioners and patients' behavior [22, 71–80]. Guidelines do not implement by themselves (or by decree!) [73]. Publishing a guideline is not enough to produce sustained changes in clinical management [81]. Weingarten stated that "a well-intentioned society puts together a wonderful guideline…they publish it in a journal, and that's where it ends [82]." Implementation requires time, enthusiasm, and resources. There is no single effective way to ensure their use in practice, dissemination, and implementation requires multifaceted interventions [81].

Low rates of adoption of internationally praised guidelines for chronic diseases like diabetes exemplify the complexities of implementation. Profiling (identifying the right person willing to implement a clinical guideline) and detailing (training, support, and follow-up) are still essential. In 1992, Grol described a series of views to change behavior [73]:

- Awareness about their existence, interest, and commitment
- Understanding its purpose and contents, recognizing personal gaps or deficiencies, and the need to change and improve
- A positive attitude; confidence in performance and success
- Initial and sustained implementation "in the real world," identification and addressing barriers and obstacles [73]

Table 23.2 Approaches to changing clinical practice

Approach	Theories	Focus	Strategy and interventions
Internal processes	Adult learning	Intrinsic professional motivation	Local consensus Interactive learning in small groups Problem-based learning
Epidemiologic	Cognitive	Information seeking, decision-making	Evidence-based guideline development Disseminating research findings through courses, mailing, journals
Marketing	Health promotion, innovation, social marketing	Adapt to the needs of target audience	Needs assessment adapt change proposals to local needs Stepwise approach Dissemination through diverse channels (mass media, personal)
Behavioral	Learning	Control by external stimuli	Audit and feedback Reminders, monitoring Economic incentives, sanctions
Social interaction	Social learning and innovation, based on social influence/power	Influence of significant peers/role models	Peer review in local networks Outreach visits, individual instruction Opinion leaders Key people in social networks Patient-mediated interventions
Organizational	Management and system	Structural and organizational conditions to improve care	Reengineering the process of care Total quality management/continuous quality improvement Team building Enhancing leadership Change structures, tasks
Coercive	Economic power and learning	Control and pressure, external motivation	Regulations, laws Budgeting, contracting Licensing, accreditation Complaints/legal procedures

Adapted from Grol [90]

An extensive review about implementation of CPG in pulmonary medicine addressed the complexities of physician's behavior and the influence of background, ethics, beliefs, and exposure to countless formal and informal guidelines as part of professional training [81–92]. One of these articles stated that (1) education in small doses is ineffective, because it pales in comparison with previous years or decades of physician education; (2) traditional methods of passive dissemination are unsuccessful to effect behavior change; (3) multiple strategies are more effective than isolated interventions; (4) implementation "by decree" doesn't work; (5) reminders have shown to be effective; and (6) disregard of situational and environmental factors, structure, and process deficiencies in health care and the delusion that guidelines by themselves "will improve the situation" are very frequent [84].

Grol and colleagues published a classical report about professional barriers to implement CPG in which they described approaches to change physician behavior (Table 23.2) [93]:

In their conclusions, they stated that "when people are planning changes, they often adopt a naïve and opportunistic attitude…a strategy is usually chosen quickly and often does not produce the expected results…our understanding of the crucial processes determining whether change will be achieved is still limited [93]."

CPG and Implementation Science

Despite the limited impact and the waste of time and resources of national standards, norms, regulations, and traditional methods of continuing medical education, consensus conferences, these faulty strategies are still preferred and supported [94]. Development, implementation, and evaluation of national CPG are complex tasks. Local adaptation and effective implementation are keys to success [95]. Gagliardi and colleagues developed and implemented a format that would influence the use of CPG and examine their contents and dissemination [96]. They found that encouraging their use involves:

1. Easy access
2. Authorship familiarity and trustworthy
3. Short and concise recommendations

4. Additional tools such as checklists, standard orders, summaries, algorithms, diagrams, color-coded tabs, pocket cards
5. Printed and electronic formats
6. Strong supporting evidence
7. Flexibility of recommendations to the local context
8. Suitability to patient's needs and preferences; auxiliary documents for patients such as leaflets
9. Clinical vignettes describing patient needs and preferences
10. Explicit resource implications
11. Tools to collect evaluative data [96]

In 2013, Grol and colleagues published a review about the effects of implementation on quality of health care [97]. In the basic principles of their landmark book, they stated that changes in organization of institutions or practices are very important, but improvement of agents of change, including doctors and health professionals, is essential to improve the quality of health care [97]. In 2017, the American College of Cardiology and the American Heart Association reviewed the evidence from the published implementation science literature to identify enhancing the adoption and implementation of clinical practice guidelines and established three categories to characterize the effectiveness of interventions [98]:

1. Generally effective for which more than two thirds of reviewed studies had positive intervention results.
2. Mixed effectiveness, in which one third to two thirds of studies showed positive effects.
3. Generally ineffective, of which less than one third of reviewed studies showed positive effects.

The overall effectiveness of four types of interventions included in 55 systematic reviews and overviews analyzed in the study was as follows [98]:

- Educational outreach visits: generally effective for both process of care and clinical effectiveness.
- Audit and feedback: generally effective for both process of care and clinical effectiveness.
- Reminders: mixed effectiveness for process of care and general ineffectiveness for clinical outcomes.
- Provider incentives: mixed effectiveness for both.
- Modified from [98].

The authors conclude that guideline implementation interventions are effective for both process of care and clinical outcomes, albeit limitations persist about their effectiveness at reducing costs [98]. Additional research and evidence about implementation in the real world are essential.

Crossing the Professional Abyss

Despite the enthusiasm behind the creation of countless CPG, a large level of unwarranted variation in clinical practice persists even when guidelines based on reputable evidence are available [99]. CPG frequently do not affect clinical practice or health outcomes. A national survey of a random sample of members of the American College of Physicians showed that although physicians recognized their potential benefits, many were concerned about their possible effects on clinical autonomy, healthcare costs, and satisfaction with clinical practice [100]. Many physicians argue that CPG are being used for cost containment, instead, to improve the quality of care [95, 101]. The potential inability of guidelines to be translated to clinical practice undermines their role as strategies for quality improvement, cost containment, and health system reform [101].

Multiple studies have confirmed the lack of adherence to CPG by physicians and their failure to change clinical practice [102]. Frolkis and colleagues showed that physicians are poorly compliant with CPG for cholesterol control even in patients at high risk of coronary heart disease [103]. Only 50% of the time they requested LDL cholesterol measurements, and screening for additional cardiovascular risk factors (hypertension, smoking, diabetes) was suboptimal, and many patients remained untreated [103]. In a similar recent report, Arnold et al. described the use of evidence-based therapies for secondary prevention in a large US cohort of patients with prior myocardial infarction and high levels of LDL cholesterol who were treated by cardiologists (46%), primary care physicians (45%), and other specialists (9%) [104]. Among 1546 patients, the authors identified "a number of concerning gaps in secondary prevention," and prescription rates are high at discharge, but the intensity of preventative therapies tended to wane over time because of a combination of clinical decisions and patient nonpersistence [104]. Choudry and associates showed an inverse relationship between the number of years in clinical practice and quality of care: more experience is not associated with better clinical outcomes [105]. Implementation is low, professional compliance is inadequate, and long-term follow-up is limited [106–109]. Despite these shortcomings, decisive, clear-cut guidance about the successful implementation of CPGs is "surprisingly little," and the knowledge gap regarding the effectiveness of CPGs on patient outcomes is substantial [110]. If patients will benefit from the results of clinical trials, the existing gap (or abyss) between evidence and clinical practice must be reduced. Unfortunately, multiple weaknesses occur at this stage [109]. Medical factors or barriers reducing adoption or compliance with CPG include [111–114]:

1. Disregard by physicians and health professionals expected to implement them, lack of familiarity or awareness
2. The conservative nature of physicians, including the innovation itself, communication channels, length of time, and characteristics of members of the social environment
3. Individualistic physician judgment resulting in:
   (a) Lack of agreement with specific guidelines
   (b) Lack of agreement with guidelines in general
   (c) Lack of outcome expectancy
   (d) Lack of self-efficacy
   (e) Lack of motivation, clinical inertia
4. Autonomous groups reluctant to introduce innovations or improvements
5. Wandering teams, loss or absence of leadership
6. Overemphasis on the guideline and failure to consider implementation
7. Deficiencies in implementation, poor planning, or communication
8. Deficiencies of healthcare systems
9. Fragmented information, fragmented groups, or institutions
10. Lack of time, poor allocation of resources, lack of resources
11. Patient factors
    (a) Changes in clinical status
    (b) Patient preferences
12. Plain refusal, "loose cannons"
13. Undetermined reasons

Adoption of CPGs depends on (1) awareness and knowledge about their existence; (2) agreement and self-efficacy; (3) complexities in structure and process; (4) frequency of reminders; (5) self-reported effect in personal versus actual performance and outcomes, measurable improvements in quality of health care; (6) incentives; and (7) removal of disincentives [100, 115–118]. To succeed, physicians, health professionals, and institutions must participate actively in the development of guidelines and commit to their use, and patients should be aware and willing to follow their recommendations [117]. Their main potential benefit is their capacity to improve the outcomes of medical care through intermediate steps of changing knowledge, attitudes, and behavior. Adherence to CPG involves a dynamic process influenced by multiple contextual factors, including barriers and facilitators previously discussed [117].

The development of CPG has become crucial. They are familiar components of clinical practice, but they also have potential benefits and harms [118, 119]. Rigorously developed, evidence-based guidelines minimize potential harms and improve the quality of health care [119]. The worldwide interest is based on a series of challenges to healthcare systems: (1) increasing demand and costs of technologies and treatment; (2) lack of applicability to address relevant issues of clinical practice included comorbidities, safety, and risk management; multidisciplinary collaboration; effect on costs or compliance; and patient self-care; (3) persistence of unwarranted variations in clinical practice; (4) clinical inertia, the fact that even when evidence is available, final recommendations often reflect personal opinions, local culture, or vested interests of developers or sponsors; and (5) the intrinsic desire to offer the best possible care [119, 120]. Expectations on their impact depend on the variety of people involved in their implementation including clinicians, patients, payers, administrators, and politicians, but their main goal is still to improve the quality of care [121]. Their main potential risk is to be inaccurate or erroneous, with resulting harms to patients and everyone [119]. CPG are criticized when they become "cookbook recipes" in disregard of the variability of clinical situations [119, 122, 123]. In addition of their use to assess clinical effectiveness, CPG also have ethical consequences: either as instruments to direct medical ethics or because their coercive enforcement for other reasons than the patients' benefit [124, 125]. Beyond their increase, CPG have not eclipsed traditional paradigms based on individual expertise [126, 127]. Guidelines are important to improve patient care, but innovations are essential to make them relevant and effective [126]. "Without these changes, they will be seen as expensive but unhelpful and ineffective toys for a happy few [120]."

Evidence-Based Medicine and CPG

> "Evidence from modern research has a lot to say about the management of diabetes mellitus"
> R. Brian Haynes and Hertzel C. Gerstein [127]

Changing Approaches of Diabetes Guidelines

Two pathways converged in the ascent of CPG for diabetes management: the surge of CPG in the 1980s and the collection of evidence with the mega-trials on secondary prevention. In 1989, the American Diabetes Association (ADA) published the first version of its "Standards of Medical Care for Patients with Diabetes Mellitus" which over three decades has become the most highly referenced [128]. The first edition of the ADA's standards included basic medical care for the initial visit, continuing care, intercurrent illness, special considerations for hyperglycemic crises, hypoglycemia, pregnancy, hypertension, chronic complications and foot care, and a brief comment for children and adolescents [128]. Management in pregnancy and in the elderly was not included [128]. Three years later, the Expert Committee of

the Canadian Diabetes Advisory Board published its clinical practice guidelines for the treatment of diabetes which were more extensive, included definition and classification, and a list of patient-centered goals of care [129]. Besides glycemic targets, the 1992 Canadian diabetes guidelines established the following goals: (1) alleviation of symptoms, (2) prevention and treatment of acute and long-term complications, (3) promoting self-care, (4) treating accompanying disorders, (5) quality of life improvement, and (6) reducing morbidity and mortality associated with diabetes [129]. The Canadian guideline emphasized the responsibilities of primary care physicians to diagnose and help patients to attain goals, educate, and motivate them and coordinate care and referrals [129]. It included explanations about diagnosis and management in adults, children, and adolescents; the elderly; native Canadians; and pregnancy become the first guideline presenting a comprehensive, patient-centered approach to diabetes care [129].

Evidence-Based Medicine and Diabetes Guidelines

The first version of a grading system for clinical recommendations appeared in the first report of the Canadian Task Force (CTF) on the Periodic Health Examination in 1979 [130]. Starting in 2002, the American Diabetes Association Standards of Medical Care included a grading system modeled "after existing methods" which were not described in the text [131]. Within its natural chronological evolution, the Canadian Task Force grading system became a benchmark to establish three major categories of evidence to assess the effectiveness of interventions [129]:

- I or A: Evidence obtained from randomized controlled trials
- II or B: Evidence obtained from cohort studies
- III or D: Opinions of respected authorities, clinical experiences, descriptive studies or expert consensus

In which I, II, and III refer to the CTF, ABD represents the ADA grading systems. The ADA included a C level for evidence obtained from poorly controlled or uncontrolled studies [131].

Evolution of Diabetes Guidelines

After three decades, diabetes guidelines expanded their scope and aligned in methodology. Management of hyperglycemia continued to be a priority, as reflected in the highly referenced algorithm published by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [132]. The ADA/EASD algorithm established a "general" glycemic goal below 7.0% based on the results of benchmark controlled clinical trials, like the Diabetes Control and Complications Trial (DCCT), the Stockholm Diabetes Intervention Study, the UK Prospective Diabetes Study (UKPDS), and the Kumamoto Study, which demonstrated that decreasing glycemia effectively reduced microvascular and neuropathic complications [133]. The ADA/EASD algorithm included a brief discussion about lifestyle interventions and a detailed review of the antidiabetic drugs available in the United States, Canada, and Europe, one algorithm to initiate and adjust insulin regimens, and another "for metabolic management" with focus on pharmacologic alternatives to achieve A1c goals [133]. The 2009 version of the ADA/EASD algorithm and recent guidelines from other countries maintain glycemic control as the main goal. Table 23.3 presents glycemic targets for adults with type 2 diabetes from several highly referenced institutions [134–140]:

Patient-Centeredness and CPG

In 2012, the ADA and the EASD updated their position statement to recognize that glycemic control needs to be pursued within a multifactorial reduction framework and that aggressive management of cardiovascular risk factors would have more benefits [141]. Based on the results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) [142], the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) [143], and the Veterans Affairs Diabetes Trial (VADT) [144] showing that not everyone benefits from aggressive glucose management, the 2012 ADA/EASD position statement stressed the importance of individualizing treatment targets [141]. Glycemic targets could be more stringent in newly diagnosed, highly motivated, resourceful adherent patients with excellent self-care capabilities, low risk of hypoglycemia, long life expectancy, absence of comorbidities, and vascular complications, while less stringent efforts should be applied to less motivated, non-adherent patients with poor self-care capabilities, high risk of hypoglycemia, long-standing disease, short life expectancy, severe comorbidities and vascular complications, and limited resources [141]. Clinical decisions should also address patients' values and desires [141]. In the following year, the ADA convened an expert forum to discuss the concept of personalized medicine in the wake of the 2012 ADA/EASD position statement [145]. The authors recognized that patients' preferences, life expectancy, disease duration, comorbidities, socioeconomic status, and cognitive abilities play a role in the selection of therapeutic

Table 23.3 Targets for glycemic control for adults with type 2 diabetes

Year	Organization and reference	HbA1c	Fasting or preprandial blood glucose	Postprandial blood glucose
2017	International Diabetes Federation [129]	<7.0%: A target between 7.5% and 8.0% may be appropriate Patients using multiple medications, with reduced life expectancy, cognitive impairment, chronic kidney disease, severe cardiovascular disease or multiple comorbidities: Values above 8.0% are unacceptable		
2018	American College of Physicians: Clinical Guidelines Committee [130]	1. Personalize goals for glycemic control based on benefits and harms of pharmacotherapy, patients' preferences, general health, life expectancy, treatment burden, and costs of care (a) Aim to achieve an A1c level between 7.0% and 8.0% in most patients (b) Consider de-intensifying pharmacologic therapy in patients achieving A1c levels <6.5% Minimize symptoms of hyperglycemia, avoid targeting an A1c level in patients with reduced life expectancy, living in nursing homes, or with severe chronic conditions	NA	NA
2018	Diabetes Canada [131]	<6.5%: To reduce the risk of chronic kidney disease and retinopathy if at low risk of hypoglycemia ≤*7.0%*: *Most adults with type 1 or type 2 diabetes* 7.1–8.5%: *Functionally dependent: 7.1–8.0%* Recurrent severe hypoglycemia and/or hypoglycemia unawareness: *7.1–8.5%* Limited life expectancy: *7.1–8.5%* Frail elderly and/or with dementia: *7.1–8.5%* *Avoid higher HbA1c to reduce the risk of symptomatic hyperglycemia and acute and chronic complications*	70–126 mg/dL	90–180 mg/dL
2020	National Institute of Clinical Excellence NICE UK [132]	Adults managed by lifestyle and diet or lifestyle and diet combined with a single drug not associated with hypoglycemia: 6.5% Adults on a drug associated with hypoglycemia: 7.0% Consider relaxing the HbA1c target on an individual basis Particular consideration for the elderly and frail with reduced life expectancy, and for people at high risk of the consequences of hypoglycemia including: Risk of falls Impaired awareness of hypoglycemia Operators of machinery Significant comorbidities Encourage patients who achieve lower HbA1c levels without experiencing hypoglycemia to maintain them	NA	NA
2020	American Association of Clinical Endocrinology [133]	Patients without concurrent serious illness and low hypoglycemic risk: ≤6.5% Patients with concurrent serious illness and at risk for hypoglycemia: >6.5%		
2020	Joslin Diabetes Center [134]	For most patients to reduce the risk of long-term complications of diabetes: <7.0% Alternative goals may be set based upon the presence or absence of microvascular and/or cardiovascular complications, hypoglycemic unawareness, cognitive status, and life expectancy For patients with long-standing type 2 diabetes, preexisting cardiovascular disease or high coronary artery risk, revisit goals to avoid adverse consequences including hypoglycemia	80–130 mg/dL	<180 mg/dL
2021	American Diabetes Association [135]	Patients without concurrent serious illness and at low hypoglycemic risk: ≤6.5% Patients with concurrent serious illness and at risk for hypoglycemia: >6.5% Pregnant women without significant hypoglycemia: <7.0% If using ambulatory glucose profile: Time in range: >70% Time below range: <4% Less stringent goals <8% for patients with limited life expectancy or if harms of treatment are greater than benefits	<130 mg/dL	<180 mg/dL

options and targets and concluded that "one size does not fit all" and patient-centered care and standardized algorithmic management are conflicting approaches but that they can be made more compatible by recognizing instances in which personalized HbA1c targets and clinical circumstances requiring co-management by primary care and specialty clinicians are warranted [145]. From this approach, HbA1c targets range from <7.0% in healthy, motivated, and resourceful patients to 7.5–8.5% in patients with social and educational issues, comorbidities, and complications [145]. Trends to recognize the preeminence of persons with diabetes in the outcomes started changing a paradigm that until recently was focused on glycemic targets and selecting the right medication regardless of costs that even the best candidates from the clinical standpoint are unable to pursue or cannot afford.

The Evidence Behind Diabetes Guidelines

During the last three decades, the importance to address all the components of CPG, including validity, reliability, reproducibility, clinical applicability, clarity, multidisciplinary process, review, and documentation, has been emphasized [146]. Guidelines had to adhere to increasingly tougher standards of transparency and objectivity and to adopt consistent formats to make them accessible for clinicians and patients [147]. These requirements are essential to guarantee that they are trustworthy because they set the standard for medical practice, influencing clinical decisions about patients, practice measures, coverage, and reimbursement [148]. Two pathways converged to establish the reliability of CPG: the AGREE II instrument [149, 150] and the Institute of Medicine standards for trustworthiness of clinical practice guidelines [30]. As in other clinical disciplines, diabetes guidelines have been carefully reviewed and appraised [188, 191, 192]. Reviews by Mülhauser and Meyer [146] and Vigersky [151] showed that:

1. Diabetes guidelines have lower scores compared with guidelines about other chronic diseases.
2. Diabetes guidelines show substantial variations in methodological quality.
3. The role of evidence versus expert opinion remains obscure in most diabetes guidelines.
4. Multiple algorithm complexities including (a) lack of evidence about selected HbA1c cutoff points, (b) lack of evidence about the effectiveness of starting triple therapy in disregard of the risk of drug interactions, (c) underestimation of the effectiveness of lifestyle interventions, (d) rapid obsolescence, and (e) disregard of out-of-pocket costs and the near equivalent effectiveness of most classes of therapeutic agents.
5. Absence of peer review. According to the ADA, "once written by the panel, a consensus statement is not subject to subsequent review and does not represent the official Association opinion."
6. The most reputed diabetes guidelines fell short of the idea in key respects including grading of evidence, complexity of algorithms, stratification of patients, disregard of costs, inflexible glucose targets, absence of peer review, and conflicts of interest.

Quality of Evidence of Diabetes Guidelines

In 2015, the ADA stated that 51% of the recommendations supporting their standards of medical care were based on higher-level evidence, and nearly half of recommendations were still of lower level [152]. Two recent systematic reviews confirm this statement [153, 154]. Bouchonville and colleagues reviewed all clinical trials with hard cardiovascular (CVD) endpoints cited in the 2016 ADA guidelines and additional studies to analyze CVD endpoints that were omitted in the ADA guidelines [153]. Analysis of 42 studies showed limitations to interpret the available evidence about the impact of glycemic control on CVD and mortality [153]. The authors state (1) that it is difficult to ascertain to what extent the reported benefits of glycemic control might be attributable to specific lowering agents or to additional reductions in blood pressure and body composition; (2) observation time of many of these studies is insufficient to draw conclusions about CVD events and mortality; and (3) current multifaceted standards for CVD reduction introduce confounding to control groups when endpoints are affected by other factors independent of glycemic control [153]. In their recommendations, the authors state that "while treatment of individual risk factors in isolation is not associated with proven benefits…treatment of multiple risk factors improves CVD outcomes in people with diabetes [153]". Kruse and Vassar performed a systematic review to analyze their Fragility Index (FI) and the Fragility Quotient (FQ) of all the randomized controlled trials referenced in the 2017 ADA Standards of Medical Care [154]. The results of 35 out of 172 analyzed studies showed low risks of bias, overall low robustness, and modest FI and FQ levels; this means that only 16 events were required to reverse the significance of a given result [154]. Loss of follow-up is also important: lost participants may have provided enough data to sway the statistical signifi-

cance of the trials, rendering the result nonsignificant [154]. Their conclusion is compelling: simply collecting the data on participants who were lost to follow-up could alter not only the results of the study but ultimately *the recommendations guiding treatment* [154]. "If we truly aspire to bring evidence based rather than authority-based medicine to clinical decisions, CPG must be the product of explicit, rigorous, scientific processes; few are" [155]. Most recommendations intended to optimize diabetes care are still developed by consensus-based panels that move us back toward authority-based medicine [155].

Conflict of Interest, Magnitude, and Consequences

Of all these issues, probably conflict of interest is the most common. In a review of disclosures, 100% percent of members of the AACE guideline group had conflicts of interest in 2011, compared with 83% in 2010. A similar review showed that 100% of the ADA/EASD had conflicts of interest in 2011 compared with 83% in the previous year [156]. To address this situation, Bennett and colleagues published a systematic review to assess whether guidelines about oral antidiabetics are consistent with current evidence and if consistency of guidelines depends on the quality of guideline development [156]. Two reviewers screened citations to identify English-language guidelines on oral medications for type 2 diabetes in the United States, Canada, and the United Kingdom [156]. The authors assessed if diabetes guidelines addressed and agreed with seven evidence-based conclusions and independently rated their quality using the AGREE instrument (Box 23.1) [157]. The results showed that: (1) 11 out of 1118 guidelines met the inclusion criteria; (2) only 3 were peer reviewed, (3) most of them made recommendations based on combinations of expert opinion and literature review; (4) the rigor of development using AGREE summary scores ranged from 0% to 100%; (5) the risk of bias using the AGREE independence domain items showed summary scores ranging from 8.3% to 100.0%; (6) 6 of the 11 guidelines reported conflicts of interest among guideline development members; and (7) guidelines with lower editorial independence scores had also lower rigor of development scores, whereas those with higher quality scores scored higher in both domains [156]. Brems et al. conducted a retrospective review of conflict of interest (COI) policies from organizations that published five or more CPGs between January 2018 and December 2019, and they found that 67% violated the COI standard [157]. Conflict of interest jeopardizes the validity of CPG and is still highly prevalent [157].

Box 23.1 Items of the AGREE II Instrument

Domain	Item or question
Scope and purpose	1. The objectives of the guideline are specifically described 2. Health questions specifically described 3. The population to whom the guideline is meant to be applied is specifically described
Stakeholder involvement	4. The guideline development group includes persons from all the relevant professional groups 5. Views and preferences of target population have been pursued 6. Target users of the guideline are clearly defined
Rigor of development	7. Evidence obtained by systematic methods 8. Criteria for selecting evidence clearly described 9. Strength and limitations of evidence clearly described 10. Methods for formulating recommendations clearly described 11. Health benefits, side effects, and risks considered in the recommendations 12. Explicit link between recommendations and supporting evidence 13. External peer review before publication 14. Updating procedure
Clarity of presentation	15. Specific, nonambiguous recommendations 16. Management options clearly described 17. Key recommendations easily identifiable
Applicability	18. Facilitators and barriers to implementation 19. Advice and/or tools to put into practice the recommendations 20. Potential resource implications 21. Monitoring or auditing criteria
Editorial independence	22. The guideline is not influenced by the views of the funding source 23. Competing interests of guideline group members recorded and addressed
Guideline assessment	24. Overall quality rating 25. I would recommend it

Modified from [158]

The Quest for Quality in Diabetes Guidelines

The AGREE Instrument has become the gold standard to appraise the quality of clinical practice guidelines for many disciplines, including type 2 diabetes [158]. Anwer and colleagues assessed the quality of type 2 diabetes guidelines using the AGREE II Instrument [159]. The final analysis included seven guidelines and showed that the two domains with highest scores were (1) scope and purpose and (4) clarity of presentation. Dominion 3, rigor of development, scored high in three guidelines, and dominion 3, applicability (implementation), scored high in three guidelines, and six guidelines declared editorial independence. Overall, one

guideline was recommended without changes, and six were recommended as long as they were modified according to the healthcare context in which they would be implemented [159]. The study confirmed the need of clinicians to recognize high-quality, trustworthy diabetes guidelines among the huge amount of available guidelines and the importance of the AGREE II Instrument in their design [159]. To support these claims, Ng and Verma assessed the quality of diabetes CPGs, and they found that the scaled domain percentages from highest to lowest were clarity of presentation (81.2%), scope and purpose (77.1%), stakeholder involvement (52.8%), applicability (42.9%), rigor of development (41.5%), and editorial independence (35.1%) [160]. The methodological quality of diabetes guidelines continues to be disappointingly low and needs to be improved for the benefit of all clinicians, stakeholders, and patients [161]. At the global level, these shortcomings have also been documented. The evaluation of quality of 17 diabetes GPGs from Europe, Canada, the United States, Australia, and Latin America by Barcelo et al. showed that ten guidelines scored ≥70% according to the AGREE II instrument, and seven guidelines scored ≥80%, with a wide range from 21% for the guideline authored by Nicaragua's Ministry of Health to 100% for the guideline developed by the National Institute of Clinical Excellence in the United Kingdom [162]. Further improvements are required in the development of CPGs to improve their effect on quality of diabetes care [162].

Diabetes Guidelines and the Real World

High-quality diabetes guidelines and evidence-based medicine are not a guarantee to improve clinical practice. Adherence rates to diabetes guidelines and clinical inertia among physicians continue to be very low 20 years after it was addressed by El-Kebbi and colleagues [163]. Less than 50% of patients treated by general physicians receive eye examinations, electrocardiograms, HbA1c measurements, and microalbuminuria screenings [164]. Wide gaps in the awareness about their existence, acceptance, and adherence prevail, resulting in wide variations of care, not just from region to region, but between primary and secondary care, even in the same region [165]. Variation in the use of CPGs diabetes ranges from 86 to 90% in Australia and Greece to 10–17% in Nigeria and Mexico [166–169].

Despite positive attitudes toward guidelines, their use is limited; only one third of clinicians report using them often or very often [170, 171]. Disconnection between primary care physicians' perceptions about the use of diabetes guidelines has extensive negative effects on clinical practice and referrals to diabetes self-care education programs [171]. Even at teaching hospitals, treatment targets for HbA1c, blood pressure, and LDL cholesterol are frequently not met [172]. Noncompliance with CPGs is as high as 70% and occurs across disciplines and countries [173]. Even in countries with longstanding traditions in the design and implementation of clinical guidelines like the Netherlands, 35% of primary care physicians reported difficulties in changing personal routines and 6% admitted to being resistant adhering with clinical guidelines [174]. Arguments to explain physician noncompliance with CPG include lack of awareness, complexity, disagreement with contents, overconfidence, time pressures, difficulties to change clinical practice, and fragmentation of care [174]. On the other hand, adherence to diabetes guidelines by patients is very low [175, 176]. Patients and their familiar circumstance are decisive for the success of GPGs but paradoxically they are usually unaware about their existence. Shared decision-making and mutual agreement is the desired endpoints of CPGs implementation [110]. It occurs when patients and their healthcare providers make joint decisions about healthcare interventions based on the best evidence and supported by preferences, values, clinical judgment, and local context [110]. To increase the effectiveness of diabetes guidelines, patients' values and beliefs should not be underestimated [177].

Strategies to implement and improve adherence to diabetes guidelines involve multifaceted interventions directed to practitioners, health professionals, and patients such as audit, feedback, training, and problem-based learning [178–180]. In combination, these interventions have shown significant improvements in adherence to diabetes guidelines and the process of diabetes care. Advances in the implementation of diabetes guidelines have been achieved mainly in Australia, the United States, and Europe [166, 167, 181]. Challenges persist in most other regions largely due to deficiencies in health systems which negatively impact adherence and implementation [182]. Hashmi and Khan described and classified factors affecting the implementation and adherence to diabetes guidelines including (a) factors related to the intrinsic attributes of the guidelines (validity, reliability, applicability) and the process of implementation (dissemination to stakeholders), (b) physician-related factors (attitude, motivation, training, incentives, coordination, goal setting), (c) patient-related factors (disease-related comorbidities, health beliefs, anxiety, depression, diabetes distress, relationship with providers and medical systems, economic constraints, refusal), and (d) health system factors (infrastructure, financial resources, policies, organization setup) [182].

In support of this statement, Owalabi et al. carried out a systematic review to compare type 2 diabetes guidelines in low- and middle-resource countries (LMIC) versus high-income countries (HIC), and they found that most LMIC guidelines were inadequate in terms of applicability, clarity, and dissemination plan, as well as socioeconomic and ethical context [183]. LMIC guidelines are mainly targeted to health professionals, and only the minority includes patients (7%), payers (11%), and policy-makers (18%)

[183]. Most guidelines from LMIC comply with less than half of the IOM standards [183]. Beyond their usefulness as reminders to prescribe medications, diabetes clinical guidelines will have to change their approach to improve outcomes.

Beyond Glycemic Targets and the Role of Patients

Diabetes outpatient management is complex and goes beyond glycemic targets. The analysis of the Steno-2 study confirmed that intensified multifactorial intervention is more effective to slow progression of retinopathy, nephropathy, and neuropathy; macro- and microvascular events; and cardiovascular and overall mortality; increases median life length over 22 years follow-up; and is more cost-effective than conventional treatment in terms of life-years gained and health benefits [184–189]. Resources for self-monitoring of blood glucose and communication technologies for patient coaching and support are valuable tools to intensify and adjust diabetes management. By comparison, type 2 diabetes management algorithms establish rational sequences for introducing, adjusting, or intensifying pharmacologic alternatives, reinforcing the need to wait and contributing to clinical inertia [190]. One key barrier to treatment intensification is lack of communication between patients and physicians that would allow patients to understand the consequences of diagnosis and engage in treatment [182, 191]. Despite the recognized role of patients in the outcomes, their involvement in guidelines is poor; information about lifestyle changes; and diabetes education and nutrition counseling are scarce or absent in type 2 diabetes guidelines [192, 193]. The third standard of the Institutes of Health emphasizes that guideline development groups should include populations impacted by the guideline and states that "patient and public involvement should be facilitated by including a current or former patient and a patient advocate or patient/consumer organization representative on the guideline development group [191]".

The Role of Comorbidities

The ascent of comorbidities in persons with diabetes is increasingly frequent, and feasible strategies have to be implemented. Some, like cancer or heart failure, are clearly dominant and influential over every aspect of diabetes care and life expectancy [194]. The importance of comorbidities has been recognized and recently discussed in diabetes guidelines [195]. Until recently, diabetes guidelines have targeted the disease in isolation. Single-disease CPGs are not designed to consider patients with multiple chronic conditions or multi-morbidity, and the alternative of applying multiple CPGs to a single patient is time-consuming, costly, and disruptive [196]. In caring for people with comorbidities, it would be more helpful to develop guidelines that summarized and cross-reference all the possible recommendations to a particular patient beyond and in addition to medications [195, 197]. To address these challenges, precision medicine is an innovative, appealing approach [197, 198]. With precision medicine, doctors and health professionals adopt more accurate treatment and prevention strategies and consider individual differences instead of the one-size-fits-all approach [197]. Precision health care involves patient care preferences, patient-oriented care, evidence-based care and self-management, and the building blocks of diabetes success [197].

Comorbidities will become more frequent as the population ages and survival from acute disease improves [195]. Developing diabetes guidelines has become increasingly challenging: treatment algorithms need to be personalized and comprehensive at the same time; the traditional glucose-centered approach is disconnected with the realities and demands of clinical practice [199]. Although seemingly impossible, new approaches have shown that it is feasible to create personalized, down-to-earth CPG for type 2 diabetes [200]. The CPG Committee of the American College of Physicians (ACP) and the US Department of Defense recently presented two innovative approaches: instead of glycemic targets, the first statement of the ACP guidance recommends that "clinicians should personalize goals for glycemic control on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden and costs of care" [201]. Addressing these usually "invisible" factors is decisive to at least explore the possibility that patients will accept and adhere to clinical recommendations. The clinical guideline of the US Department of Veterans provides a detailed algorithm in which before deciding the first pharmacologic alternative, glycemic control should take into consideration the patient's age, reproductive status, comorbidities (including an extensive list of the most important), adverse effects and contraindications of medications, history of severe hyper or hypoglycemia, social determinants of health, and providing diabetes education "that patients understand" [201]. Moving forward, the consensus report for Management of Hyperglycemia of the American Diabetes Association and the European Association for the Study of Diabetes provides a patient-centered decision cycle involving (1) assessing patient characteristics, (2) specific factors that impact choice of treatment, (3) shared decision-making to create a management plan, (4) agree on management plan, (5) implementing the management plan, (6) ongoing monitoring and support, and (7) review and agree on the management plan with patients [132].

Conclusions

Traditional ABCs of management (A1c, blood pressure, cholesterol) should also include additional essential elements of care: (D) diabetes education, (E) eye examinations, (F) foot examination, (G) glucose monitoring, (H) health maintenance, and (I) indications for special care [202]. Traditional diabetes guidelines stress that patients should receive health care from interdisciplinary teams including physicians, nurse practitioners, physician assistants, nurses, dietitians, exercise specialists, pharmacists, dentists, podiatrists, and mental health professionals, and patients must assume an active role in their care. Fulfilling these recommendations escapes the realities of everyday diabetes care, even in developed, more resourceful countries like Switzerland, where 32% of patients with type 1 diabetes and 44% achieve A1c levels below 7.0% and low levels of LDL cholesterol [203]. Implementing diabetes guidelines is still the big challenge, the gap, or the abyss to achieve their expected results in the real world; even high-quality CPGs have room for improvement in terms of implementation [204]. Continuing support for implementation of diabetes guidelines among primary care practitioners is essential to improve the perspectives and reduce the suffering of the increasingly large number of persons with diabetes. In conclusion, room for improvement for diabetes clinical guidelines is everywhere [205, 206].

Multiple Choice Questions

1. According to the American Diabetes Association guideline, the goal for HbA1c levels in patients with type 2 diabetes is:
   (a) <6.0%
   (b) <6.5%
   (c) **<7.0%**
   (d) <7.5%
   (e) <8.0%
2. According to the American Association of Clinical Endocrinologists guideline, the goal for blood pressure in patients with diabetes is:
   (a) ≤140/90 mmHg
   (b) <140/80 mmHg
   (c) <130/90 mmHg
   (d) **<130/80 mmHg**
   (e) <120/80 mmHg
3. According to the Joslin Guideline, the goal for LDL cholesterol in patients with type 2 diabetes and atherosclerotic cardiovascular disease is:
   (a) **<70 mg/dL**
   (b) <100 mg/dL
   (c) <130 mg/dL
   (d) <160 mg/dL
   (e) <200 mg/dL
4. One of the primary goals of clinical guidelines is:
   (a) To promote the use of new medications
   (b) To establish medical consensus
   (c) To increase medical knowledge
   (d) To create norms to be followed
   (e) **To improve the quality of health care**
5. In order to improve the quality of care, clinical guidelines pursue:
   (a) **Reducing the unjustified variation of medical care**
   (b) Guaranteeing obtaining the necessary resources
   (c) Treating all patients in tertiary care facilities
   (d) Total patients' compliance
   (e) Reinforcing the role of physicians in chronic care management
6. One major challenge of clinical guidelines is:
   (a) **Adoption and implementation**
   (b) Compliance of patients
   (c) Obtaining the required resources
   (d) All of the above
   (e) None of the above
7. Successful implementation of clinical guidelines is associated with all of the following, except:
   (a) Awareness about its existence
   (b) Understanding its purpose and contents
   (c) Recognition of personal gaps and deficiencies
   (d) **Publication in a leading medical journal**
   (e) Confidence in performance and success
8. Encouraging the use of clinical guidelines involves:
   (a) Easy access
   (b) Additional tools including checklists or algorithms
   (c) Strong supporting evidence
   (d) Flexibility of recommendations to the local context
   (e) **All of the above**
9. Medical factors or barriers reducing adoption of clinical guidelines include:
   (a) Disregard of physicians expected to implement them
   (b) The conservative nature of physicians
   (c) Autonomy and reluctance to innovate or improve
   (d) Absence of leadership
   (e) **All of the above**
10. Most diabetes guidelines:
    (a) Are high-quality, evidenced-based
    (b) Are high-quality, consensus-based
    (c) Are medium-quality, evidence-based
    (d) Are low-quality, evidence-based
    (e) **Are low-quality, consensus based**

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Measuring Diabetes Quality of Care: Clinical Outcomes, Cost-Effectiveness, and Patient Experience of Care

24

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Chapter Objectives

- To discuss advantages and challenges of measuring outpatient diabetes care quality.
- To identify and discuss key quality measures for outpatient diabetes care including single-domain and composite measures of glucose, blood pressure (BP), lipids, weight, tobacco use, and appropriate use of antithrombotic medications.
- To identify emerging opportunities and challenges related to assessment of patient experience of care, shared decision-making, and burden of treatment.
- To discuss factors that influence the cost-effectiveness of diabetes care and to discuss the cost-effectiveness of diabetes case management, clinical decision support, and shared decision-making strategies.

Concluding Remarks

- Providing simple and understandable measures of diabetes care quality to clinicians, patients, and the public may be associated with improved diabetes care quality in some settings.
- Clinicians and care systems often direct available resources to improve what is measured, so selecting a narrow set of diabetes quality measures that are directly and strongly linked to major clinical outcomes is desirable.
- Recent data indicate wide variation in care quality across clinicians after adjustment for patient factors. This information can be used to guide clinician-specific quality improvement and learning interventions.
- In settings with high-quality diabetes care, there is as much as 300% variation in costs. Thus, identifying maximally cost-effective treatment pathways is an area of needed clarity.
- Improving shared decision-making and patient experience of care and reducing treatment burden may improve treatment adherence, continuity of care, and clinical outcomes.

Box 24.1 Implementing a Diabetes Composite Quality of Care Measure

- Step I: Identify all adult patients with a diagnosis of diabetes and with two or more visits to the clinic in the last 12 months. This is the denominator.
- Step II: (a) Classify each patient in the denominator as meeting or not meeting each of these five clinical goals in the past 12 months. (b) If the patient is excluded (criteria for exclusion noted below), they get credit for that clinical goal. (c) If there is no BP measure, A1c test, documentation of use of antithrombotic or lipid lowering therapy, or documentation of tobacco use status within 12 months, they are classified as not meeting that clinical goal.
  - Most recent glycated hemoglobin (A1c) measure done within 12 months is <8%.
  - Most recent systolic BP measure within 12 months is <140 mmHg.

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  - Patient is currently prescribed a moderate or high-dose statin or other lipid-lowering medication. (Exclude: LDL < 100 mg/dL, documented lipid-lowering medication intolerance; women of child-bearing potential.)
  - If the patient has diagnosed atherosclerotic cardiovascular disease, they are taking daily antithrombotic medication. (Exclude: those with no prior diagnosis of cardiovascular disease and those at high risk of gastrointestinal bleed.)
  - Chart documentation that the patient is currently a nonsmoker.
- Step III: The patent is counted in the numerator only if they meet all five clinical goals as specified.
- Step IV: Divide the numerator by the denominator and multiply by 100 to calculate the percentage of diabetes patients at the composite diabetes goal.
- Step V: This measure can be used (a) to compare quality of diabetes care across care systems, clinics, clinicians, or groups of patients, and (b) to inform patient or payer selection of preferred clinicians based on quality of care. Adjustment of results based on patient factors (such as age, race, sex, education, income, or insurance status) may be considered.

Introduction

It is widely recognized worldwide that the quality of care provided to those with diabetes mellitus is far from optimal. To guide quality improvement efforts in an efficient way, it is important to identify and target key aspects of diabetes care, track valid measures of care quality over time, and use these measures to direct improvement efforts and assess their results. Here we will discuss the strengths and weaknesses of current measures of diabetes care quality and comment on current challenges that face those engaged in this effort, including developers of quality measures, users of such measures to improve clinical care delivery, or users of such measures to monitor population health. For the sake of brevity, we will focus on outpatient care of adults with type 2 diabetes and limit our attention in this chapter to selected measures of clinical outcomes, cost of care, and patient care experience.

Measuring Clinical Quality of Care: Accountability Versus Improvement Measures

Data from the United States suggest that diabetes leads to about a 5 year loss of life expectancy and a 10 year loss of disability-free life expectancy [1, 2]. A key question for both clinicians and public health leaders is to identify effective prevention or treatment strategies that mitigate these losses both at the population level and for each individual patient.

The most effective way to mitigate the loss of life expectancy and disability-free life expectancy from diabetes is to prevent or delay the onset of type 2 diabetes. This is the topic of several chapters in this book. It is clear from large randomized trials such as the Diabetes Prevention Program and similar programs in Scandinavia and China that both lifestyle interventions and certain pharmacologic agents are somewhat effective in this regard [3, 4]. It is clear that primary prevention of type 2 diabetes should be a very high priority for both clinicians and public health policy makers, and studies to improve the effectiveness of both lifestyle and pharmacologic interventions to prevent diabetes are needed [5].

Once a patient develops type 2 diabetes, the question becomes how to prevent or delay downstream diabetes-related complications and mitigate the adverse impact that diabetes often has on length and quality of life. Microvascular complications such as retinopathy (that may lead to blindness), nephropathy (that may lead to dialysis or renal transplantation), and neuropathy (which may cause pain and lead to falls or amputations) affect a high proportion of adults with type 2 diabetes. The occurrence of these microvascular complications typically increases with the duration of diabetes and is often accelerated by tobacco use and by inadequate control of glucose and blood pressure. However, while trials of intensive glucose and blood pressure (BP) control have shown some benefit on delaying the onset and progression of these microvascular complications, there is little hard evidence to show an impact on reduced rates of the end-stage microvascular complications such as blindness, end-stage renal disease (ESRD), or amputation [6–8]. Moreover, lifetime occurrence of these three end-stage microvascular complications is much lower than is the lifetime risk of a fatal or nonfatal macrovascular complications of myocardial infarction or stroke in adults with type 2 diabetes [1, 2].

The occurrence of macrovascular complications of myocardial infarction and stroke in those with diabetes has been improving in the last 20 years but is still about twice as high as in those without diabetes. These major cardiovascular events account for the majority of excess deaths and excess costs attributable to type 2 diabetes [9, 10]. Thus, in measuring quality of diabetes care, control of multiple major risk factors that are the principal drivers of microvascular and especially macrovascular complications should be the focus of clinical and public health attention.

In recent years, a composite quality measure often used to assess care of adults with diabetes consists of the proportion of diabetes patients who simultaneously meet all five of these clinical measures: adequate BP control, glucose control, and tobacco control, plus appropriate use of lipid medications and antithrombotic medications. Many experts

support this "composite measure" of these five clinical domains, calculated as the proportion of diabetes patients seen at least twice in 12 months in a given care system who meet these five measures (based on most recent measure available within the 12-month period): nonsmoker, A1c < 8%, BP < 140/90 mmHg, on lipid medication if tolerated, and on antithrombotic medication such as asprin (which applies only to patients with atherosclerotic cardiovascular disease) [11]. Box 24.1 below describes how this composite measure can be computed and used.

When a diabetes composite measure was first introduced in 2003 in the United States, less than 5% of US adults with diabetes had all five components at the goals proposed in Box 24.1. The proportion of diabetes patients with all five components at these proposed goals rose to about 30% in the United States by 2015–2018 [12], with major variation from less than 5% to about over 50% across care delivery systems, clinics, individual clinicians, and subgroups of patients. Levels of risk factor control are significantly lower in younger adults versus older adults and lower for Blacks, Latinos, and Native Americans compared to non-Latino Whites. With the onset of the COVID-19 pandemic, there has been a decrease in the proportion of diabetes patients meeting these composite quality measure goals, mostly due to decreased A1c and BP measurement related to reduced access to care [13].

There are several factors to consider when comparing clinicians, clinics, or delivery systems performance using various diabetes or other clinical quality measures. First, if the goal is to incent clinicians to improve care, it may be important to adjust content and interpretation of quality measures based on (a) socioeconomic or clinical characteristics of patients, and (b) availability of technology such as A1c testing available at primary care facilities [14–16]. Otherwise, facilities with less access to technology and/or clinicians who take care of low income or less educated patients (who may have more difficulty getting to clinical goals for a variety of reasons) will be penalized by the quality measures. This issue is especially important if quality measures are publicly reported or if performance on the quality measures is linked to financial compensation [15]. The counter argument is that adjusting quality measure thresholds based on patient characteristics may lead to a double standard of care, with implicit acceptance of lower quality care for more challenging patient populations.

Another consideration related to use of a composite quality measures is whether to weight the components of the composite measure equally or unequally. Are they all equally important? The impact of BP control, lipid control, and tobacco control on life expectancy and major cardiovascular (CV) events in those with diabetes has historically been much greater than the impact of glucose control, unless glucose control is especially poor [17–20]. However, some research suggests that not only the most recent values, but also past values of A1c, BP, lipids, and tobacco use may impact subsequent health outcomes [21]. Moreover, the relative benefit of improving A1c, BP, lipid, or tobacco control varies across patients; in general, the further from goal a patient is on a given measure the greater the potential benefit after effective control is achieved.

These considerations would favor a weighted approach to quality measures, with the weight of each component of the composite measure proportional to the potential benefit of that component. Ideally, the weights should vary based on the clinical circumstances of an individual patient (in some patients, control of very high A1c may confer the most benefit). Technology to enable prioritization of treatment options for individual patients with and without diabetes has recently become available [22–25]. However, the use of individualized care quality measures, although logical and potentially useful, is complex to operationalize and therefore has not yet been widely used. As this science matures, it may be possible to measure diabetes quality at the patient level not only by achievement of threshold levels of A1c, BP, or lipid control but also by estimating change over time in a patient's CV risk, using equations such as the American College of Cardiology/American Heart Association (ACC/AHA) CV disease risk equations, the UKPDS Outcome Model 2 prediction equations, or a combination of these [26, 27].

Just as there is wide variation across clinicians, medical groups, and care delivery system in composite measures of diabetes care quality, so too there is wide variations in the five specific components of the composite measure. For example, some clinicians do a better job with BP control than with glucose control. There are few studies that investigate in detail this variation at the clinician level in patterns of risk factor control. Some of the variation is likely attributable to variation in patients' health literacy, numeracy, or overall educational or poverty level. Thus, when assessing variation in diabetes care quality across clinicians and delivery systems, some experts suggest that credibility requires that the analysis be adjusted for differences in patient characteristics.

Another factor linked to variation in quality of diabetes care is a long delay in clinician recognition or management of changing levels of glucose, BP, lipids, or other clinical parameters. Deterioration in glucose control, for example, may be due to progression of diabetes, nonadherence to medications, lapses in dietary practices, stress, occult infections, or other factors. When patients well-controlled on glucose, BP, or lipids deteriorate, clinicians who delay addressing the underlying reasons and adjust pharmacotherapy if needed in a timely way will, on average, have lower proportions of their diabetes patients at goal. Delayed adjustment in treatment, often referred to as "clinical inertia," is associated with poor clinician performance on key measures of diabetes quality of care and adverse clinical outcomes [28]. Quality measures that assess clinical inertia have been

proposed by some but are time consuming to measure and report and may not adequately consider patient-related financial, social, and psychological constraints that sometimes present barriers to optimal care [29–31].

There are hundreds of "evidence-based" components of diabetes care, but not all are of equal benefit to a given patient at a given point in time, and the strength of the supporting evidence from randomized trials varies widely. Thus, all evidence-based aspects of diabetes care are *not* suitable for selection as quality measures. It is best to focus attention on clinical domains that need improvement, have a major direct impact on important health outcomes, have affordable and available management strategies, and can be easily measured.

It is also important to keep in mind that once a clinical quality measure is adopted as a publicly reported accountability measure, clinicians and health care systems tend to narrowly focus on measuring and improving that aspect of care. This can lead to unintended consequences. For example, in the 1990s in the United States, the first publicly reported diabetes quality measure was retinopathy screening—because in the pre-electronic medical record era, it could be accurately and inexpensively measured from insurance claims data. Delivery systems devoted immense resources to improving eye exam rates, while largely ignoring poor glucose or BP control—clinical factors that cause retinopathy. That early quality measure may well have *increased* the prevalence of retinopathy by drawing attention away from glucose and BP control.

Thus, we propose a small core set of "accountability measures" that can be used to publicly report diabetes care quality, and a larger set of "improvement measures" that are not publicly reported, but that can be used privately by clinicians and care delivery organizations, as needed, to improve care by pinpointing specific barriers to higher quality diabetes care.

If a clinician, clinic, or care system is doing poorly on *accountability measures* such as those listed in Box 24.1, it may be helpful to deploy a set of more detailed *improvement measures* to identify care improvement opportunities related to glucose, BP, lipid, or other clinical goals. Improvement measures are designed to (a) identify *why* a particular clinician may have suboptimal accountability measures and (b) point to clinician-specific or clinic-specific "care improvement opportunities" that can reasonably be expected to improve quality of care. Prior work provides some empiric support for this approach [32, 33].

Clinicians with similar levels of performance on accountability measures may have substantially different patterns in associated improvement measures. This observed variation in patterns of care across clinicians is illustrated in Table 24.1 and suggests the potential usefulness of tailoring quality improvement and learning strategies to clinician-specific "care improvement opportunities." The definition of a "care improvement opportunity" for a specific clinician may be as simple as identifying performance on improvement measures relative to the median of their peer group's performance (Table 24.2). In settings where electronic health records or other sophisticated health information technology is available, collecting detailed clinical data on specific patterns of care at the clinician level is increasingly feasible.

When improvement measures are assessed, it is important to consider how best to share such information with clinicians, clinic leaders, or others. Several characteristics increase the effectiveness of feedback, such as timeliness, regularity over time, positive feedback alongside feedback on sub-optimal performance, feedback to a supervisor as well as the front-line clinician, providing feedback in both

Table 24.1 Examples of variation in percentages of PCC-specific care improvement opportunities (CIOs) in study-eligible patients from a larger algorithmically defined set. Columns represent the percentage of patients with each CIO within PCC percentiles, and a ratio of COIs in 90th to 10th percentile PCCs

CIO topic	CIO description	10th	25th	50th	75th	90th	Ratio
Thiazide diuretic under use	% of patients with uncontrolled BP and adequate renal function not on a thiazide	16.3	18.9	23.1	27.6	30.3	1.9
ACEI/ARB under use	% of patients with uncontrolled BP who are not on ACEI/ARB use	13.7	15.5	20.0	24.7	27.9	2.0
Use of 3 or more BP medications	% of patients with uncontrolled BP on three or more medications	1.0	1.9	3.0	4.3	6.0	6.1
Hypertension recognition	% of patients meeting BP criteria without a problem list diagnosis	9.6	12.6	16.0	19.4	23.9	2.5
Use of moderate or high intensity statins when indicated	% of patients meeting ACC/AHA criteria for statin use with ASCVD risk ≥10% on less than moderate intensity statin	12.6	16.3	23.7	32.3	42.9	3.4
Statin initiation when indicated	% of patients meeting ACC/AHA criteria for statin use but not on a statin	17.1	21.2	27.8	37.3	47.5	2.8
Antithrombotic underuse	% of patients meeting criteria for antithrombotic use, but not on an antithrombotic	7.5	9.5	13.0	18.2	22.3	3.0
Antithrombotic overuse	% of patients not meeting criteria for antithrombotic use, but on an antithrombotic	5.0	6.3	9.5	12.3	15.9	3.2
Screening for diabetes when indicated	% of patients meeting USPSTF criteria for diabetes screening without tests in 3 years	6.5	9.2	12.6	17.0	20.3	3.1

Abbreviations: *CIO* care improvement opportunity, *PCC* primary care clinician, *BP* blood pressure, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ACC/AHA* American College of Cardiology/American Heart Association, *ASCVD* atherosclerotic cardiovascular disease, *USPSTF* United States Preventive Service Task Force

Table 24.2 Prototype content of PPF feedback to PCC and their supervisor, updated every 2 months

Selected care improvement opportunity (CIO) from a set of 30	You're doing better than this % of PCP peers	Number of patients evaluated in past 2 months	% of your patients with opportunity to improve care	
			You now	Your goal[a]
Use thiazide diuretics	8	50	38%	23%
Initiate statin treatment when indicated	11	24	35%	28%
Refer smokers to cessation programs	23	14	24%	16%
Hypertension recognition	71	61	12%	☺ Great job!
Screening for diabetes when indicated	83	33	9%	☺ Great job!
Antithrombotic underuse	94	17	8%	☺ Great job!

[a] This is performance level of median PCC

verbal and written form, feedback that is actionable, and setting specific goals for improvement with repeat measurement to assess progress [34]. In a time of widespread clinician and health worker burnout, feedback must be provided as sensitively as possible.

Measuring Patient Experience of Care

Diabetes is a complex chronic disease, and clinicians are faced with the daunting challenge of dealing with a myriad of effects that diabetes may have on many dimensions of a patient's life. In addition to its direct biological, psychological, and financial impact on patients, diabetes also may significantly impact the family, friends, employers, and caregivers of those with the illness. The social and economic impact of diabetes on direct medical care costs, indirect costs, and workforce productivity is also substantial. A fundamental question related to measurement of diabetes quality of care is this: how wide a net do we want to cast? Can we hold the care delivery system accountable for the myriad impact of diabetes on a person's life? Should governments, employers, schools, or nursing homes be held accountable for accommodating the needs of those with diabetes?

There is increasing attention to integration of health care with behavioral health and social services for vulnerable persons or families, which would include many individuals or families affected by diabetes. Diabetes may be associated with increased work absenteeism or presenteeism, decreased income, high medication costs, high health-care costs, and decreases in physical, emotional, and social function. The strongest evidence exists for integration of psychological and diabetes care in models such as Collaborative Care [35]. In many communities, social services are available to provide necessary assistance with income, housing, food, safety, or health-care costs. However, integration of social services with primary health care services is often incomplete, and better access to and coordination of services is often needed [36, 37]. Although integration of health-care services and behavioral health and social services may be beneficial for many patients with diabetes, holding clinicians or clinics responsible for delivery of integrated services may not be well accepted by some clinicians and may not be feasible in some rural or under-resourced areas. Moreover, quality measures that assess integration and coordination of care are not yet fully developed and validated.

Quality measures that focus on *patient experience of care* are now being used in some care delivery systems. Important aspects of patient experience of care include a timely access to necessary health-care services, clear and comprehensible communication from clinicians, an active role in care decisions, and satisfaction with clinical care provided.

Collecting patient-reported information on experience of care, patient-centered care, or shared decision-making may require surveys, conversations, electronic communication, and analysis of verbal or questionnaire data. This can be quite time consuming and expensive. Although representative random sampling of patients may reduce the resources required for such measures, accuracy may be compromised if sampling is done in a biased way, if response rates are low, or if the sample size is insufficient to draw reliable conclusions.

Nonetheless, a number of survey instruments have been reasonably well validated to measure patients' experience of care, diabetes distress (Problem Areas in Diabetes/PAID), patient-centered care, shared decision-making, and self-efficacy (Diabetes Empowerment Scale/DES); some of these are available in validated Spanish versions [38–40].

Shared Decision-Making and Treatment Burden

Shared decision-making (SDM) can be informally defined as timely sharing of information between patients and clinicians that empowers patients to actively participate (if so desired) in selecting from a set of evidence-based treatment options, those that best reflect their values and personal preferences. Shared decision-making is an intrinsic and necessary part of primary care practice but is often neglected [41]. One study found that primary care clinicians provided basic information on newly prescribed medications—the name of the medication, frequency of dosing, duration of use,

intended benefits, and major side effects—only about 20% of the time [42]. This lack of basic information precludes shared decision-making and has been linked to low medication adherence and increased mortality in some studies [21]. The impact of shared decision-making on diabetes-related clinical outcomes is an area of active research [43].

Some thought leaders have recently proposed that treatment regimens be designed to minimize the burden of care imposed on the patient by their diabetes treatment [44]. This is a neglected but important aspect of care; the typical adult with diabetes takes seven to eight medications a day in the United States, and glucose monitoring, dietary considerations, and frequent office visits increase time and resources devoted to diabetes care [45, 46]. For example, treatment with insulin often imposes burdens related to blood glucose monitoring, disruption of daily routines, risks of hypoglycemia, and high out-of-pocket costs for insulin and associated supplies and equipment. Use of sophisticated insulin delivery systems and continuous glucose monitoring may confer clinical benefits for some patients, while adding different care requirements, concerns, and expense. Some data suggest that minimizing the burden of care may improve treatment adherence, timely follow-up care, and reduce patient stress [44, 47]. For these reasons, some experts suggest that measuring burden of care is justified and that development of creative strategies to minimize burden of care may improve care, adherence, and long-term clinical outcomes [48].

Shared decision-making may help reduce the burden of care [49] and can be used to develop individualized care goals and care plans for complex patients [50–52]. Note that quality measurement becomes more complicated if it must accommodate patient-specific clinical goals. One possible solution to this problem is to select clinical goals for quality measure that are more generalizable, such as an A1c goal of <8% rather than A1c<7%, to accommodate patient-specific variation in clinical goals [53, 54].

It is of particular concern that many clinicians (and patients) overestimate treatment benefits, often by an order of magnitude. For example, in the UKPDS, intensive glucose treatment for about 18 years led to an additional 90–180 days of quality-adjusted life [55]. In the ACCORD randomized trial, intensive glucose control significantly increased death rates by 18–20% compared to moderate glucose control [17, 56]. How many patients, with this information in mind, would opt for intensive glucose treatment using the medications available when those studies were conducted? Fortunately, newer classes of drugs such as GLP-1RA and SGLT2i appear to confer impressive clinical benefits on many diabetes patients who also have cardiovascular disease, chronic kidney disease, or congestive heart failure [57, 58].

These considerations underscore the complexity of shared decision-making and patient-centered care. That complexity has led to increased interest in use of web-based decision support algorithms and risk equations that can be used to accurately estimate and compare the potential benefits of various evidence-based treatment options for a specific patient [59]. Observing and understanding the treatment preferences of well-informed patients can, in turn, improve our understanding of what factors influence treatment preferences and lead to improved approaches to shared decision-making [22, 23, 25, 60].

Measuring Affordability and Cost-Effectiveness of Diabetes Care

Several studies document that health-care costs of those with diabetes are more than double the health-care costs of age- and sex-matched patients without diabetes [9]. Higher costs are driven by several factors, including pharmaceutical and equipment costs, more outpatient visits, and more frequent and longer hospitalizations across a wide range of admission diagnoses [61]. From the clinical point of view, the major driver of excess, potentially avoidable costs is major cardiovascular events, including admissions for congestive heart failure, myocardial infarction, stroke, peripheral arterial disease, and revascularization procedures.

Although cost of care is generally higher for those with diabetes, studies indicate that there is a wide variation in costs of care not only across patients but also across care delivery systems for similar patients. This has led many experts to speculate that more attention should be devoted to identifying optimal "care pathways" that combine clinical success with low costs. For example, suppose a patient requires two glucose-lowering agents to achieve their evidence-based glucose goal, the cost to the care delivery system (insurer or government) for various combinations of effective glucose-lowering medications may vary as much as 50-fold with generic metformin and sulfonylureas being least expensive, and SGLT2i and GLP-1RA being most expensive drug classes. Likewise, out-of-pocket cost to the patient may vary widely by care system and insurance arrangements [62].

Insulin acquisition costs are another example of variability in cost to the delivery system, and in some cases to patients. Recent analysis indicates up to tenfold variation in insulin costs in the United States based on the type of insulin (human vs. analog) and delivery system (vial versus cartridges). Thus, judicious use of analog insulins, perhaps reserving them for patients at high risk of serious hypoglycemia, could be a policy that substantially lowers costs [63–65].

The analysis of cost-effectiveness in diabetes care is even more complicated. The threshold of costs per quality-adjusted life year (QALY) that purchasers are willing to pay

varies substantially by country, by payer, and by year. The cost of complications such as an amputation or myocardial infarction also varies greatly across nations and across delivery systems within nations. Moreover, pharmaceutical corporations may agree to very different acquisition costs for a given medication in different countries, and within some countries, in different delivery systems. All these factors complicate efforts to accurately estimate cost-effectiveness of diabetes care across time, nations, and delivery systems.

Despite challenges, it is instructive for delivery systems to estimate cost per QALY gained, for various treatment pathways (human vs. analog insulin, vials vs. pen insulin delivery systems, use vs. nonuse of continuous glucose monitoring in stable type 2 diabetes, expensive vs. less expensive non-insulin glucose-lowering drugs, various lipid lowering treatment strategies, various visit intervals, in-person vs. virtual clinical encounters). Doing so and using these data to identify optimal treatment pathways for various groups of diabetes patients, and to aggressively negotiate drug acquisition costs with suppliers, may well reduce the cost and improve the cost-effectiveness of diabetes care in some clinically defined groups of patients.

The recent demonstration that selected GLP-1 receptor agonists (GLP-1RA) and SGLT2 inhibitors may significantly reduce major CV events and CV mortality and preserve renal function, which will complicate efforts to assess optimal treatment pathways from the cost and cost-effectiveness point of view. The cost-effectiveness of these new medication classes will be driven both by their clinical benefits and by their variable but generally high acquisition costs. Also, important to consider are cost-sharing arrangements with patients, whose ability to afford substantial out-of-pocket costs typically varies widely by income.

At the population level, a certain fraction of diabetes patients will require intensive interventions to achieve and maintain glucose, BP, and lipid care goals. Intensive interventions that can be deployed in a targeted way across a population of diabetes patients and can range from intensive, individual level interventions such as nurse case management combined with peer-led, collaborative diabetes education and self-management training to web-based clinical decision support delivered through the electronic health record at primary care encounters. Diabetes care management including diabetes self-management education and peer support is more expensive at the individual level but has been shown to produce more significant improvements in clinical risk factors including A1c [66–68]. Clinical decision support requires a substantial initial investment, but that can be spread over a large population resulting in low individual level costs, although with smaller clinical effects. These two intervention strategies have been shown to be similarly cost-effective and can be used in a coordinated, complementary way [69].

Finally, it is important to note that the cost-effectiveness of type 2 diabetes prevention has been thoroughly studied and in most scenarios is either cost saving or highly cost-effective, whether accomplished via lifestyle change programs or by using medications such as metformin [70]. Very few things in health care are cost saving, so investments in type 2 diabetes prevention programs is increasingly recognized as a good investment by various private and public care delivery systems [71].

Summary

Systematic measurement of diabetes care quality can identify important gaps in clinical care, map variation in quality of care across clinicians and delivery systems, and provide useful information to guide care improvement efforts. A wide range of diabetes quality measures are available. Selection of a parsimonious set of *accountability measures* that are causally related to key clinical outcomes is a top priority. A larger set of optional *improvement measures* can be used to map care improvement opportunities that, if addressed, will improve accountability measures. Measures that assess patient experience of care, shared decision-making, and cost of care may also be considered. However, resources needed for quality measures can be considerable and may reduce resources available for direct patient care. Measures that can be extracted from electronic clinical databases are generally much less expensive than measures that require patient-reported data. Ongoing efforts are needed to optimize diabetes quality measures and develop new measures of patient-centered care, efficient use of resources, and patient-reported outcomes and to identify effective strategies for primary prevention of type 2 diabetes.

Multiple Choice Questions

1. Clinical measures that are causally related to major microvascular and macrovascular diabetes complications are often selected for clinical quality of care measures. Such clinical measures might include all the following except:
   (a) Antithrombotic use
   (b) Cholesterol control
   (c) Blood pressure control
   (d) **Annual diabetes patient education**
   (e) Glucose control
   (f) Nonuse of tobacco

   Comment: Diabetes patient education is extremely important, but in randomized trials it has only a marginal impact on glucose, BP, lipid, or tobacco control and is not casually related to lower rates of major diabetes complications. Thus, the other aspects of care listed here are more suitable for diabetes quality of care measures.

2. Regarding the cost-effectiveness of electronic health record (EHR)-linked clinical decision support and diabetes case management, which of the following statements is false:
   (a) Case management is much more expensive on a per-patient basis,
   (b) Over the long run, clinical decision support may be cost-saving.
   (c) They are about equally cost-effective.
   (d) **Most patients resist active case management as an invasion of privacy.**
   (e) Clinical decision support has high initial implementation costs.

   Comment: In large studies of diabetes case management, about 2/3 of high-risk diabetes patients engage in the case management process.
3. Reasons to measure diabetes care quality at the clinician level include all the following except:
   (a) There is significant variation in patterns of care at the clinician level.
   (b) **It is often difficult to link individual patients to a single responsible clinician.**
   (c) Many clinicians like to know how they are doing compared to their peers.
   (d) Such information can guide clinician-specific learning interventions.
   (e) Electronic data make this easier to do than in the past.

   Comment: Well over 90% of patients can be linked to a usual primary care clinician in most health care systems, based on frequency of visits with various clinicians and/or patient designation of a usual primary care clinician in electronic health record systems.
4. Which one of the following statements about the relationship of outpatient cost of diabetes care to outpatient quality of diabetes care is false:
   (a) Quality of care is not related to cost of care at the clinic level.
   (b) **High-quality care costs more.**
   (c) Low-quality care can be as expensive as high-quality care.
   (d) Cost of care is important both to the patient and to the care delivery system.
   (e) Costs of care vary widely across patients with diabetes.

   Comment: There is abundant evidence that there is not a strong association of outpatient costs of diabetes care with quality of outpatient diabetes care.

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Further Reading

O'Connor PJ, Bodkin NL, Fradkin J, Glasgow RE, Greenfield S, Gregg E, et al. Diabetes performance measures: current status and future directions. Diabetes Care. 2011;34(7):1651–9. [This article presents an overview of important issues and choices related to measuring diabetes quality of care, with author perspectives representing a wide range of stakeholders.]

Greenfield S, Kaplan SH, Ware JE Jr, Yano EM, Frank HJ. Patients' participation in medical care: effects on blood sugar control and quality of life in diabetes. J Gen Intern Med. 1988;3(5):448–57. [This pivotal article showed that patient-centered care and shared decision making are linked to better glucose control, higher satisfaction with care, and better quality of life for adults with diabetes. Electronic health record (EHR)-linked clinical decision support systems can process patient-specific date, identify evidence-based care options, and present care options to both the patient and clinician at the point of care, enabling more efficient and consistent shared decision making.]

Challenges to Diabetes Care Innovation. The Case of a Major Public Institution in Mexico

25

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Introduction

Type 2 diabetes (T2D) affects 9.4 million adults aged 20 years and over in Mexico, equivalent to 11.3% of the total adult population, and is the second leading cause of death, contributing with 9% of the total deaths that occur in the country—100,000 per year [1, 2].

Public and private institutions and providers make up the Mexican health system and develop mostly independently health programs and innovations to address health problems and particularly diabetes. The Mexican Institute of Social Security (IMSS, its acronym in Spanish)—the largest public institution in the country—covers 31.5 million adults over 20 years—38% of the country's total—through mandatory coverage of formal private sector employees and their families. IMSS employs 17,561 general practitioner and 90,587 nurses in primary care nationwide [3]. In 2002, IMSS established PrevenIMSS, a program to address diabetes and other chronic diseases supported on screening modules in primary care clinics staffed by nurses and referring presumptively diagnosed cases to family doctors for confirmation.

From 2008, IMSS aimed to address a growing diabetes epidemic through a vertical program—DiabetIMSS—supported on specialized diabetes primary care modules staffed by a family physician, a nurse, a nutritionist, and a social worker [4]. In spite of some success in improving metabolic control, DiabetIMSS scaling up was interrupted in 2012 due to human resource and financial constraints and reached only 8% of primary care clinics and 3% of people living with diabetes [5, 6]. IMSS also went on to implement a Diabetes Clinical Practice Guideline (DCPG) in collaboration with the Ministry of Health, aiming to improve quality of care by family medicine physicians [7]. The scaling up of this guideline was also limited due to constraints in the adaptation of the guideline to local conditions and a lack of leadership at the national level by the Ministry of Health [8].

From 2017, IMSS aimed to strengthen the quality of care for the most prevalent chronic diseases, abandoning vertical efforts and relying on institutional leadership at the national level inspired in the internationally recognized Chronic Care Model (CCM) aim of improving quality, increasing coverage, and reducing cost. This was done through piloting the Chronic Disease Preventive Model (CDPM) and developing Integral Care Protocols (ICP).

CDPM is currently in a pilot phase in the state of Nuevo León and includes four strategies: risk stratification, targeting actions to specific risk groups, monitoring people in the continuum of care, and health process and impact evaluation [9, 10]. People who do not achieve metabolic control of diabetes—estimated at 30% of the total—are referred to Outpatient Metabolic Control Units (OMCU) [11]. The CDPM includes intensive diabetes education, interdisciplin-

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ary care teams, and intensification of insulin therapy and of HbA1c monitoring; all of them are key aspects to achieve effective coverage. The diabetes education model adopted by the CDPM was based on best international evidence testing various alternatives through a small-scale randomized trial [12]. Interdisciplinary care is based on previous experience demonstrating the need both to avoid specialized diabetes primary care modules and to integrate interdisciplinary care within existing resources [6] as supported by international best practices [13]. DCPM also includes an information and patient recall platform that could impact on greater screening of at-risk persons, as well as follow-up for diagnosis.

The high prevalence of diabetes, particularly in the age group of 60–79 years of age, clearly justifies integrating diabetes care within general practice. Intensification of insulin therapy is in agreement with observed high levels of diabetes complications within IMSS population and low insulin use according to international best practices. In addition, a focus on universalizing HbA1c monitoring is also congruent with best international practices [14, 15].

While CDPM innovations are highly justified, IMSS faces diverse challenges to innovation in its internal institutional context characterized by centralization and bureaucratic controls, in the external context relating the institution to its governing institutions, its financing and to the expectations of its beneficiaries, and in the processes through which innovations are developed.

This chapter presents a comprehensive overview of the CDPM implementation challenges through exploring the main coverage bottlenecks facing detection, diagnosis, and diabetes care and exploring the facilitators and barriers to the implementation of care innovations in its internal and external contexts and in its implementation process. Implementation challenges focus on four CDPM innovations: intensive education, interdisciplinary teams, intensification of insulin therapy, and HbA1c monitoring in primary care.

Data was obtained through a mixed-method approach including the review of program and research and innovation development documents; the analysis of the National Health and Nutrition Survey (ENSANUT in Spanish) of 2018 [16]; and interviews with 13 family physicians, diabetes specialists, innovation leaders and with 13 persons living with diabetes. ENSANUT was processed to identify measures of coverage and quality of care offered by IMSS in the detection, diagnosis, and treatment of diabetes. Interviews with IMSS personnel aimed to explore qualitatively the range of perceptions regarding the internal context, while interviews with persons living with diabetes aimed to assess the external context, complemented with documentary research regarding the support to innovation provided by IMSS governors. Financial constraints to diabetes care innovation were assessed through a costing exercise to assess the requirements for each of the four CDPM innovation areas within diverse scenarios of population coverage and depth of vertical scaling-up of innovations for 2030. The costing exercise enabled an assessment of the budgetary impact expected by IMSS. The detailed methods and results obtained can be consulted in published book and journal article [17, 18].

Diabetes Care Coverage Bottlenecks

IMSS provided early diabetes detection tests at least once every 3 years, according to institutional norms, to only 49% of its adult beneficiaries aged 20 years or more in 2018 [19] (Fig. 25.1, Table 25.1). Data for previous years suggest that only a fraction of beneficiaries that receive a presumptive diagnosis go on to demand confirmation through primary care consultations and lab tests, with only 26% of the total in 2014. According to national IMSS planners, the main problems limiting early detection and confirmation are that beneficiaries are not targeted according to risks such as age, weight, and family history with diabetes, and that there is poor follow-up of persons with a presumptive diagnosis [20].

The total IMSS beneficiary population aged 20 or more years living with diabetes in 2018 according to ENSANUT 2018—diagnosed or undiagnosed—was 4.13 million for a prevalence of 13.1% of adults (Table 25.1), of whom 3.87 million self-reported their condition based on previous diagnosis, and 0.26 million were discovered through testing as part of the survey. However, the burden of diabetes among IMSS beneficiaries reported by IMSS based on clinical records is higher, which amounts to 5.4 million persons for 2020. Diabetes prevalence is larger among females, with 14.9% as against 11.0% for males while the burden of diabetes is higher in the age group of 60–79 years, reaching 30.3%. According to ENSANUT, 9.1% of beneficiaries with confirmed diabetes seek care outside the institute (Fig. 25.1). However, IMSS reports a much larger treatment gap of 43% based on their own estimates of total beneficiaries living with diabetes. Beneficiaries receive at least four medical consultation per year within or outside the institute in 77.4% of cases, with a somewhat higher percentage among beneficiaries treated by IMSS, of 79.9%. The majority of beneficiaries—89.2%—receive some form of medication while 23.2% are treated with insulin. According to IMSS diabetes program officers, insulin therapy should cover 40% of the population treated; thus, current attainment is 58.0% of target.

HbA1c tests are performed only to a small proportion of persons living with diabetes, with 15% receiving two or more tests. Control of diabetes through exercise and/or diet was reported by 11.1% of IMSS beneficiaries. Beneficiaries receive good quality care in only 37.0% of cases as measured by access to a set of ten key indicators, while IMSS reports

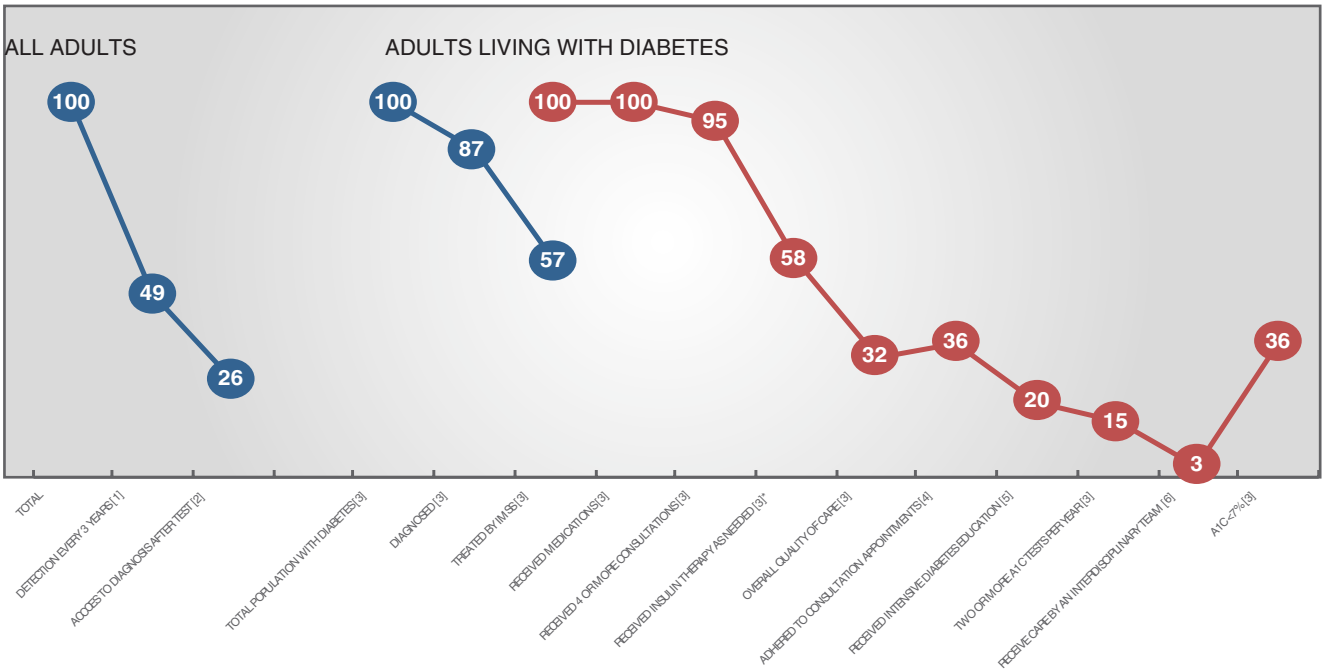

Fig. 25.1 Coverage bottlenecks for diabetes detection and control among IMSS beneficiaries. ENSANUT 2018. Data dates, notes and sources: 1: 2018, IMSS [19]. 2: 2014, Sánchez O [20]. 3: 2018, INSP [16]. 4: 2016, Cerón [21]. 5: 2019, Interview, Family Medicine Division coordinator based on patients accessing DiabetIMSS. 6: 2017, for IMSS beneficiaries having access to interdisciplinary teams in DiabetIMSS [5]. *The 32% of insulin coverage corresponds to the coverage as reported in Table 1 of 23.1% of the total beneficiaries living with diabetes against the coverage target of 40% of the total set by CDPM. Thus, 23.2%/40% = 58%

Table 25.1 Situation of diabetes and diabetes care. IMSS 2018

Persons with diabetes (total)	4,130,554
Persons with diabetes treated by IMSS (total)	3,752,965
Persons with diabetes treated by IMSS (%)	90.8
Self-reported diabetes (total)	3,874,023
Self-reported diabetes (%)	93.8
Undiagnosed diabetes (total)	256,531
Undiagnosed diabetes (%)	6.2
Prevalence of diabetes (%). Weighted	
Total	13.1
Females	14.9
Males	11
20–39 years	2.4
40–59 years	15.5
60–79 years	30.3
80– years	25
Received intervention (%). Weighted (95%CI)	
4+ visits to the doctor for diabetes control	
All beneficiaries	77.4 (77.3–77.4)
Treated by IMSS	79.9 (79.9–80)
Two or more HbA1c tests	14.5 (14.4–14.5)
Surveillance or detection of arterial hypertension	79.1 (79.1–79.2)
Cholesterol and triglycerides measurement	14.1 (14.1–14.2)
Obesity detection	12.8 (12.8–12.8)
Microalbuminuria test	18.4 (18.3–18.4)
Vision check	20.1 (20–20.1)
Foot check	31.1 (31–31.1)
Controlled with diet and exercise	11.4 (11.4–11.4)
Receive any medication	
All beneficiaries	89.2 (89.2–89.2)
Treated by IMSS	90.1 (90.1–90.2)
Overall diabetes ambulatory care quality (weighted average of ten indicators)	
All beneficiaries	36.3 (36.3–36.4)
Treated by IMSS	37.0 (36.9–37.0)
With insulin therapy	23.2 (23.2–23.3)
With controlled diabetes (HbA1c < 7%)	37.1 (37.1–37.2)
With highly uncontrolled diabetes (HbA1c > 9%)	27.0 (26.9–27.1)

Source: Instituto Nacional de Salud Pública [16]

that full adherence by patients to scheduled diabetes consultations is at 32% [21]. Diabetes education under diverse models and intensities is received by only 20% of persons living with diabetes [12] and interdisciplinary diabetes care is received by only 3% of beneficiaries, of those treated by the DiabetIMSS program.

The percentage of IMSS beneficiaries with diabetes under control as measured by the test of HbA1c below 7% is 38.1%, while up to 26.1% of beneficiaries live with highly uncontrolled diabetes as measured by HbA1c levels above

9%. The percentage of IMSS beneficiaries with levels of HbA1c < 7% is below that observed in other countries, for example in the USA, where 64% of the population is reported with HbA1c < 7% [22]. HbA1c levels across the IMSS beneficiary population thus suggest opportunities to improve glycemic control.

The most critical bottlenecks can be identified based not so much on the lowest values observed for each indicator but on the sharpest drop along the value chain of indicators. These are early detection of diabetes every 3 years and overall quality of care for persons with confirmed diabetes. While current data for the former is limited given its focus on all adults rather than those at highest risk, the drop goes from a need of 100% to 49% of coverage. In quality of care, the drop goes from 80% of persons accessing an adequate number of yearly consultations to only 37% receiving appropriate quality of care. Critical indicators as assessed according to coverage are intensive diabetes education and receiving a minimum of two HbA1c tests per year, and particularly accessing interdisciplinary care, with only 3% of coverage.

Internal Facilitators and Barriers to Innovation

IMSS is structured by levels of operational, tactical and strategic responsibility with the potential to identify problems, identify alternatives for innovation, as well as to plan responses. IMSS operates with a high degree of centralization where innovation at the local level depends on the initiatives and orders issued at the national level. According to our interviews, physicians experience centralization as limiting their capacity for decision-making for clinical care improvement.

The education of people living with diabetes tends to be vertical, reproducing centralization in management and hindering empowerment. Centralization makes it difficult for staff to coordinate with different disciplinary profiles, while mechanisms to generate professional coalitions are difficult to establish or operate. Family physicians perceived the feasibility of improving diabetes education through allocating more time for consultations, training all professional profiles to work in teams, and through increasing the awareness on the need of patient education on the part of decision-makers higher up in the hierarchy.

Training of health workers through continuous and intensive approaches is a critical aspect in the process of scaling-up innovation. IMSS operates a national health worker education and training program supported on hospital traineeships and most importantly on-line, automated short courses. For 2018 a total of 66 courses were offered, of which only three focused on diabetes care yet none had been aligned to CDPM's needs, particularly toward interdisciplinary care. Continuing education coverage across all on-line training courses and traineeships reached only 3.5% of the total IMSS health workforce in 2018. Of this total, 1.5% participated in traineeships and 2.0% in on-line courses. Training across health worker profiles varied, with 8.8% of the medical personnel having been trained, as against 2.2% of the Nursing personnel and 0.7% of other health personnel, including Social Work and Nutrition. At the current pace, it would take IMSS 11 years to train 100% of physicians in any of the currently provided health areas, 44 years in the case of Nursing and 151 years for other health personnel. Given that only 3 out of 66 courses were focused on diabetes care, training times would take 20 times longer to ensure all personnel are trained in diabetes and are thus able to participate in interdisciplinary, fully integrated diabetes care.

In spite of the paucity of training, the physicians and innovation leaders interviewed had a clear sense of urgency of the need to address major changes to ensure quality diabetes care. The levels of uncontrolled diabetes are clearly viewed as an unacceptable problem, threatening the financial collapse of IMSS. In particular, family physicians perceive as unacceptable the restrictions they live with respect to the routine use of HbA1c and the intensification of insulin therapy. They considered that the availability of the HbA1c and the training to use insulin therapy could allow them to improve the quality of care, thus reducing patient referrals and consequent delays to internists in secondary care.

However, innovation at IMSS is incompatible with the daily pressures faced by family physicians. The HbA1c test was perceived by physicians to be hampered by current standards, by the demand to speed up consultations, and particularly by the supply shortages, provoked by the perceptions, on the part of administrative personnel, of wasteful application in the absence of precise norms. In spite of higher purchases of HbA1c tests at the time of the interviews to ensure their widespread availability in primary care, physicians that were interviewed still lacked knowledge regarding its availability or the norms regulating its application. Intensive diabetes education also faces incompatibility within the institutional context, particularly with regards to family physician's productivity.

Performance incentives are recognized at the strategic level as important tools toward the attainment of quality-of-care goals. However, informants were frustrated by failures in attempts to implement them in the recent past. Performance management is limited to the occasional clinical record review while family physicians perceived that professional training provides weak incentives toward innovation, being limited to providing a certification of points per completed course. They considered that it is important to increase staff motivation by systematizing access and promotion of patient education, offering performance incentives and improving support at the strategic level.

Communication of CDPM innovation objectives and goals was perceived as weak, much as it had been in the past with the DiabetIMSS program and with the implementation of clinical guidelines. CDPM progress is being reviewed at the national level based on occasional presentations to top level authorities and leaders such as at the National Academy of Medicine, without strategies clearly in place to encourage primary care staff toward innovation. Although family physicians show willingness to learn, they perceived themselves as undervalued and poorly informed about innovations. Family physicians were insistent on the time constraints they face in their daily routines, which act as barriers to learning and impact on their capacity to put in place reflective processes.

Delays in scaling up of innovation and interruption of past innovations—in the case of DiabetIMSS—were perceived by physicians as a consequence of decision-making by officials who are insensitive to health team needs and who lack a long-term vision. While IMSS is attempting to strengthen CDPM innovation implementation through designated leaders, part-time coaches, and full-time process managers at each primary care unit, interviews and documentary evidence suggest that these resources aim to enforce discipline among health personnel rather than to promote problem solving.

IMSS shows strengths for innovation planning, particularly for the design and piloting of innovations at the national level. However, the institution's overly large size, verticality, excessive bureaucratic control, and limitation of autonomy at the local level act as significant barriers restraining staff motivation, coordination, and alignment of interests along the innovation value chain.

The most salient barriers perceived by family physicians are related to organizational factors at the strategic level. Current functional differentiation results in a pyramidal hierarchy that marks a distance between top-level staff and family physicians. While staff in planning functions at the strategic level are optimistic, family physicians expressed little enthusiasm and confidence in the capacity of upper management to bring about change.

The main barriers expressed by interviewees related to the internal context to CDPM implementation are weak communication, weak feedback strategies, and absence of performance-related incentives. Studies in other health systems have demonstrated the need for efforts to motivate staff toward the attainment of organizational objectives, something that the size and vertical nature of IMSS undoubtedly requires for success [23].

IMSS has demonstrated capacity to design and test diabetes innovations in the past, and the CDPM follows in this trend [12, 24–27]. However, innovation efforts are mostly spearheaded and organized by upper management without the participation of sector-wide actors and strategies of national and international research and innovation institutions. Such collaboration has the opportunity to introduce more rigorous development and evaluation methods.

Implementation Process Facilitators and Barriers

Research is critical for innovation given its capacity to assess with objectivity the efficacy and effectiveness of care improvements in their capacity to increase coverage and quality while controlling costs. The importance of research is attested by the international literature in the intervention areas pertinent to CDPM, where our search identified 23 research articles in the last 10 years in journals indexed in PubMed testing innovations with interdisciplinary teams, people education, intensification of insulin therapy, and use of HbA1c as a gold standard for diagnosis. Most of these articles reported on randomized controlled trials involving large populations at national level. Importantly, IMSS research teams published two articles, both focusing on testing innovations in education.

An article by Gamiochipi et al. compared the effectiveness of two models of education: shared decision-making between the doctor and the person and strengthening of disease self-management.[1] While the methodology was quasi-experimental, the study did not allocate individuals to each treatment protocol in a randomized manner, while only local samples of 200 people that did not address cultural or regional variability were involved in a 6-month follow-up. The research found that self-management had a greater impact on diabetes control than shared decision-making, leading to its adoption for the intensive education component of CDPM. The second study by Pineda and collaborators tested multimedia information modules in family medicine units. This research found modest results in disease control and was not adopted in the design of the CDPM.[2]

The two published research projects undertaken by IMSS to support innovation are the product of a fairly strong research infrastructure available to the institute through its national level health research coordination. However, research focuses on small-scale testing of innovations and does not take advantage of the large size and high centralization of the institution.

[1]Gamiochipi, Mireya, Miguel Cruz, Jesús Kumate, y Niels H. Wacher. "Effect of an intensive metabolic control lifestyle intervention in type-2 diabetes patients." Patient Education and Counseling 99, núm. 7 (2016): 1184–89. https://doi.org/10.1016/j.pec.2016.01.017.

[2]Pineda Del Aguila, Ignacio, Lubia Velázquez-López, M. Victoria Goycochea-Robles, Fabiola Angulo-Angulo, and Jorge Escobedo De La Peña. "Multimedia education to support management of type 2 diabetes patients. A quasi-experimental study." Surgery and Surgeons (English Edition) 86, núm. 5 (2018): 404–11.

The CDPM includes in its design the undertaking of periodic evaluations to assess progress, identify areas for improvement, and monitor the quality of implementation. Program staff carried out a CDPM pilot to assess its impact 1 year after its implementation, using a before and after design. Even though with design limitations, the exercise showed positive results, especially regarding intensification of insulin therapy following training.

IMSS is strengthening planning of the CDPM to address the risk of scale-up interruption due to lack of resources. To establish interdisciplinary care protocols, emphasis is being given to the redefinition of professional roles rather than to new contracting. Professional training is now mandatory according to resource profiles and needs, while the above-mentioned management strategies are intended to modify professional behavior. Planning through plan-do-study-act (PDSA) cycles is driving target definition for HbA1c coverage, intensification of insulin therapy, and diabetes control. Leaders with management expertise and experience in the implementation of the CDPM are being formed to support the PDSA-based planning, as with the case of coaches mentioned above. The intensive education strategy of CDPM was developed, as mentioned above, through testing alternative models following a randomized trial published in a peer-reviewed journal and then adapted for implementation by interdisciplinary teams [12]. Loss of fidelity of these interventions during scale-up is being addressed through a supervision strategy.

The CDPM planning process has clear facilitators including process reengineering, clinical protocols, role redefinition, and an incremental approach to implementation based on the PDSA cycles already mentioned, all directed to maximize performance and reduce the need for additional resources. Another facilitator is the allocation to innovation of full-time senior managers and leaders with extensive experience and designation of innovation champions.

Facilitators and Barriers in the External Context of Innovation

The scaling-up of innovation requires support and the capacity to overcome barriers in the external institutional context, which, in the case of IMSS, includes inputs from the governing employee and employer unions through the technical council and from the user base. The IMSS Technical Council, the highest level institutional governing body, is focused above all on the general administration of the institute, with very little participation in decision-making to promote innovation toward the control of chronic diseases. Thus, between 2000 and 2019, the technical council supported only four agreement toward innovation in diabetes. The most important authorized in 2014 financing for USD 30 million for a multiannual pilot to outsource primary diabetes care with private providers. However, the initiative was canceled without reaching the award due protests by the IMSS health worker trade union. While part of this funding was reallocated to pilot the CDPM through the fully in-house initiative already described, the technical council did not participate in this reallocation, thus limiting the support this body could have given to scaling-up of this important initiative.

The perspectives regarding quality of care and trust held by IMSS beneficiaries living with diabetes present more barriers than facilitators to care innovation toward the CCM. In this model, people and health professionals would have to form symmetrical relationships characterized by mutual trust and effective control on the part of people over their care processes. The current situation, however, is characterized by the verticality of care, a distrust on the part of people toward the care processes and by their discontinuity given the participation of multiple, uncoordinated service providers within and outside IMSS (Fig. 25.2).

Beneficiaries expect IMSS to be a provider of medications rather than to be a partner in the provision of comprehensive care. This perspective suggests a "pharmacologization" of routine medical care. Our qualitative study suggests than younger beneficiaries living with diabetes do not perceive losing the right to medical care with the IMSS as a major problem, as they can find options for the supply of medicines at low cost through private sector physicians working in consulting rooms adjacent to pharmacies and subsidized through the sale of medications. Other alternatives to obtain low-cost medicines include demanding services from the Ministry of Health consulting rooms available for the uninsured or, in some cases, affiliating as a dependent of a family member with access to IMSS. However, older adults—especially those who require insulin or other medications related to diabetes complications—perceive as highly important retaining care by IMSS since they face multiple barriers to acquire the medications they need.

Another important element that must be transformed to achieve the empowerment of IMSS beneficiaries is the perception that medical services are a concession of the state and employers and not a right by virtue of their contribution. In this way, the loss of access to IMSS due to losing a contract with a formal employer, drug supply shortages, and dissatisfaction with services are accepted in many cases. Awareness of their health rights could facilitate the empowerment of people living with diabetes to self-manage their care and to demand innovation.

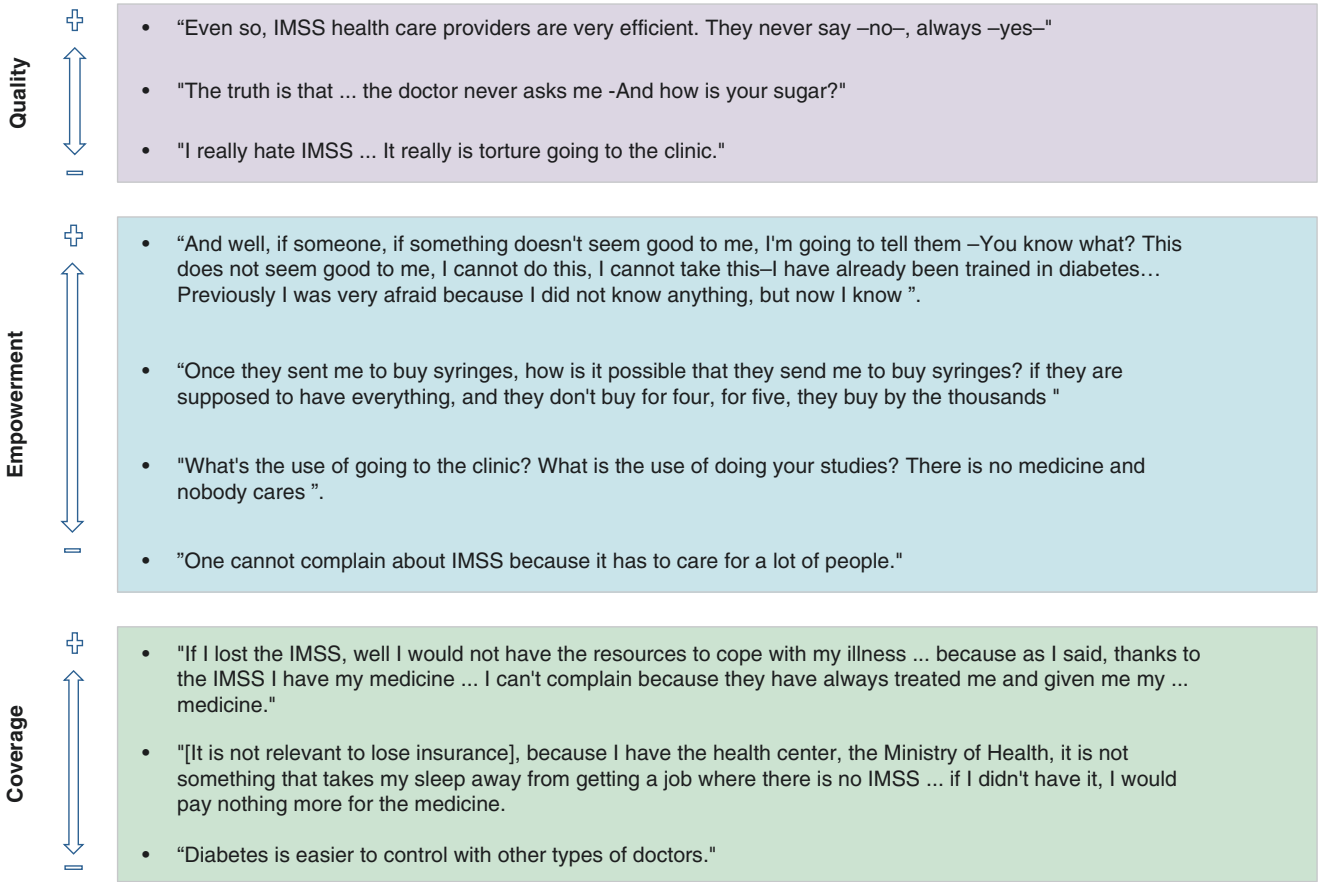

Fig. 25.2 Perceptions of IMSS beneficiaries living with diabetes. Source: Author data

Costs of Scaling-Up Innovations and Budgetary Impact

For a successful implementation and scaling-up of the CDPM and CCM, IMSS should invest in promoting beneficiary empowerment, establish interdisciplinary care teams, intensify insulin therapy, extend HbA1c monitoring, and strengthen management teams. Table 25.2 presents specific indicators to be attained within each of these five areas, identifying the current coverage and proposing implementation goals for 2030 along two scenarios: medium and high. These indicators were validated by the IMSS national diabetes management team.

Besides scaling-up innovations to the desired level (vertical coverage), IMSS should also consider expanding diabetes care coverage to reduce the number of persons living with diabetes that are not treated by the institution (horizontal coverage). Based on IMSS own figures, as noted above, the total population with diabetes is of 5.4 million, while those covered are 3.1 million for a coverage gap of 43%. Given population growth and diabetes epidemic trends, we estimated a total diabetes population of seven million for 2030. Considering the current IMSS diabetes coverage expansion rates, we expect up to 4.3 million people to be covered for 2030, still leaving a gap of 39%. Innovations should, therefore, be scaled-up not only to attain this coverage rate but also to reduce the coverage gap. We proposed reducing this gap in two scenarios for 2030: a modest reduction of 30%, which represents the treatment of an additional 0.8 million people, and an ambitious reduction of 70%, which would lead to the coverage of a total 6.2 million people.

The human resources needed to scale-up diabetes care innovations for 2030 ranges from a 3.4% increase in the total number of family physicians in a scenario of no increment in the horizontal dimension and a medium vertical coverage to 16.2% increment in the scenarios of ambitious reduction the horizontal dimension gap and high vertical coverage (Table 25.3). Indeed, given current low levels of staffing in these professional disciplines and the demands of CDPM, increments would be required at between 426% and 956% for clinical psychology in the two extreme scenarios and of 2399% and 5017% for nutriology.

The expected increments for family medicine and nursing assume maintaining today’s observed density per 1000 pop-

Table 25.2 Innovation area and indicator to scale-up the CDPM, with medium- and high-level attainment goals for 2030

Innovation	Indicator	Situation in 2019	2030 goal	
			Medium	High
Education with an intensive model for people with T2D	1. People graduated from courses	3%	50%	70%
Interdisciplinary work teams	2. Professionals who participate in care teams and who are trained	0%	100%	100%
	3. People served by teams	3%	50%	70%
Insulinization	4. People who use insulin	16%	28%	40%
	- NPH	12%	20%	25%
	- Glargine and Mix	4%	8%	15%
Control monitoring with HbA1c	5. People with 2 tests per year	14%	80%	100%
	6. Rapid tests as% of total	0%	15%	30%
Management of programs and services	7. Teams for each FMU ≥ 10 clinics	0%	50%	100%
	8. Health teams that reach the performance incentive cap	0%	30%	60%
	9. Registered people	0%	20%	70%

Source. Author data. *HbA1c* glycated hemoglobin, *T2D* type 2 diabetes, *NPH* neutral protamine hagedorn (NPH) insulin, *FMU* family medical unit

Table 25.3 Percentage increase in professional profiles to provide team care according to the CDPM required by two innovation scenarios*

Coverage gap reduction (horizontal)	Innovation scale-up (vertical)	Family medicine	Nursing	Social work	Clinical psychology	Nutriology
Current trend	Medium	3.4	0.5	-0.7	426	2399
	High	4.8	0.7	-1.0	637	3439
30%	Medium	6.8	0.6	3.4	524	2882
	High	9.3	0.8	4.7	774	4115
70%	Medium	12.1	0.7	10.2	654	3526
	High	16.2	1.0	13.6	956	5017

Increases for Family Medicine and Nursing assume maintaining current observed densities per 1000 beneficiaries among the general population
Source: Author data

ulation, which may be insufficient. Indeed, keeping the same density would imply that family physicians would have to increase their dedication to diabetes care, from 12.9% of their total contracted time up to 26%, depending on the coverage scenario (Table 25.4). While increases in nursing dedication for diabetes care would be more modest—between 2% and 4% of their total time—dedication by social work, clinical psychology, and nutrition would be between 22.4% in the case of the former and up to 100% for the latter two. Such expected increments in any scenario except doing nothing are unsustainable and point to the need to develop new professional profiles—particularly for psychology and nutrition, as well as task shifting and automation across professionals and technical personnel for all disciplines.

The costs of human resources for both patient care and management as well as those for training, beneficiary education, technology platforms, insulin, and HbA1, were calculated for the various scenarios (Table 25.5). Costs of

Table 25.4 Dedication to diabetes care (percentage of total time) of total IMSS resources according to professional profile and innovation scenario, assuming the current physician and nursing densities are maintained

Coverage gap reduction (horizontal)	Innovation scale-up (vertical)	Family medicine	Nursing	Social work	Clinical psychology	Nutriology
Current trend	Medium	12.9	2	22.4	100	100
	High	18.6	2.8	32.7	100	100
30%	Medium	15.1	2.3	26.2	100	100
	High	21.7	3.3	37.9	100	100
70%	Medium	18.1	2.8	31.2	100	100
	High	25.9	4	45	100	100

Source: Author data

Table 25.5 Cost scenarios to 2030 in diabetes care innovations according to innovation scenarios. Millions of pesos from 2019 adjusted to present value[a]

Coverage gap closure	Persons to be covered by 2030 (millions)	Level of innovation goal implementation							Δ in scale-up at High (G-A/A)
		Status quo total	Medium			High			
			Total	Additional[b]	Net[c]	Total	Additional[b]	Net[c]	
		A	B	C	D (B-1695)	E	F	G (E-1695)	
Current trend (H)	4.3	1695	5992	3629	4297	8573	5897	6878	306%
Close by 30% (I)	5.1	2010	7096	4472	5401	10146	7221	8451	320%
Close by 70% (J)	6.2	2430	8568	5671	6873	12244	9089	10549	334%
Δ in closure at 70% (J-H/H)	44%	43%	43%	56%	60%	43%	54%	53%	

Source: Author data

[a] Costs are adjusted to present value considering a discount of 3% per year

[b] Refers to differences between total and status quo costs considering only the costs of additional human resources required to increase the goals while maintaining the population density observed in 2019. Hence, additional costs do not match the total costs less the status quo costs

[c] Correspond to the difference between total costs in each scenario with respect to the costs of the status quo and current trend in coverage gap closure (shaded, $1695)

expanding low-cost oral medications in the horizontal dimension were not considered for simplicity, while it was assumed that physician and nursing densities would be kept at today's levels with the corresponding increments in the proportion of time spent to diabetes care. The costs of improving governance and attaining beneficiary empowerment and satisfaction were not included and should be considered for a more accurate estimation of the needs of implementing the CDMP.

The total additional costs estimated range from $1695 million pesos, in the scenario of current horizontal expansion and medium vertical scale-up, to $10,549 million pesos for the scenario of 70% of reduction in the horizontal gap and high level of vertical expansion of innovations. The incremental cost in each scenario with respect to the status quo (current trend in horizontal expansion without innovation) differ importantly. Scaling-up innovations to the high-coverage scenario for 2030 would require a 306% increase in diabetes care costs. However, expanding innovations while also closing the coverage gap by 70% would require incrementing costs by 335%—only 39% more than following the coverage increment in the status quo. Therefore, if such a large investment is approved, IMSS should consider improving the quality of diabetes care along with increasing horizontal coverage, considering the reductions in potential diabetes complications. If the cost increments are compared across the scenarios including high innovation goals and varying horizontal coverage—from the reduction of the coverage gap expected following current trends to a 70% reduction—then cost increases up to 53%. With this level of cost increment, both vertical and horizontal expansion goals should be targeted.

The total costs vary considerably across specific CDPM innovations, as shown in Table 25.6 for costs within the sce-

Table 25.6 Costs of innovations in care for people who will live with diabetes in the high coverage and quality scenario by 2030, covering 5.1 million people. Millions of pesos in 2019

innovation	Cost in 2019	Coverage goal	Total cost in 2030	
			$	%
1. People with T2D who participate in intensive education courses	$36	70%	$1188	10%
2.- People with T2D treated by a multidisciplinary team	$113	70%	$3758	31%
3.- DT2 training courses that include interdisciplinary work practices	$0	70%	$72	1%
4.- People with diabetes on insulin treatment	$2481	40%	$5013	41%
Monitoring with HbA1c				
5.- People with T2D who received 2 tests per year	$149	100%	$1438	12%
6.- Rapid tests as% of the total	$0	30%	$337	3%
7.- UMF with management teams	$0	100%	$107	1%
8.- Health teams with incentives to perform in T2D	$0	30%	$197	2%
9.- People with T2D registered in monitoring platforms	$0	70%	$135	1%
Total	$2778		$12244	100%

Source: Author data. Note that percentages do not add ten 100% due to rounding

nario of closure at 70% of the coverage gap and a high level of innovation implementation. Considering total costs, intensification of insulin therapy would consume 41% of total costs, followed by the establishment of interdisciplinary teams, with 31% of total costs. Importantly, training courses, monitoring platforms, management teams, and rapid tests would absorb between 1% and 3% in each case. This analysis suggests the importance of investing in pharmaceutical industry and in human resource development, while taking advantage of the relatively small but highly productive investments in the other innovation areas.

The impact that diabetes innovation costs would have on the IMSS budget can now be considered, including its benefit in reducing diabetes-related complications and their associated costs. Projecting the current levels of diabetes care, the trends in reducing beneficiary coverage gaps, and the expenditure on diabetes care reported by IMSS [28], the total 2030 spending on diabetes is expected to sum up to 14.3% of the sickness and maternity insurance (SEM) budget (Fig. 25.3). In the scenario of reducing 70% of the coverage gap without implementing innovations, diabetes care spending would represent 20.6% of the total SEM budget. However, if innovations are scaled-up at the same time to a high level, spending would only increase by 3.9%, to reach 22.8% of total SEM budget. The majority of the financial effort would thus be directed to reducing the coverage gap. Including innovations to increase quality of care, reduce morbidity and mortality, and offset hospitalization costs related to complications should be considered in order to provide better care for IMSS beneficiaries.

Diabetes-related complications are expected to represent 5.4% of SEM budget for 2030 under current trends. In the scenario of increasing only coverage without innovations, the SEM budget share expected to care for diabetes-related complications would increase to 7.8%. However, with innovations this is expected to be reduced to 6.0%.

Investing in diabetes care coverage and innovation should be considered taking into account the expected impact on quality-adjusted life years (QALYS), and hence in productivity for a population such as is the case in Mexico with a high diabetes prevalence among younger-aged persons in the labor market. Indeed, simulation of QALYS led us to expect a significant increase, from 24.54 million years among persons living with diabetes in the status quo scenario, to 32.26 million in the scenario with greatest coverage gap closure and highest innovation implementation.

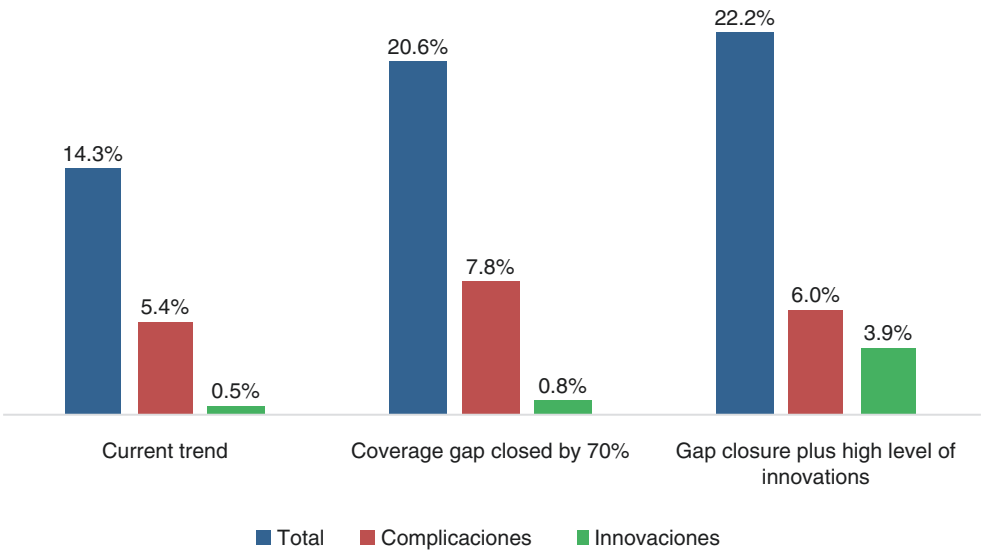

Fig. 25.3 Percentage of IMSS sickness and maternity insurance (SEM) dedicated to diabetes care in 2030 under the status quo and high coverage and quality scenarios by type of care. Source: Author data

Discussion

Being the largest and public health institution in Mexico, IMSS exemplifies well the opportunities as well as the challenges to adopt and scale-up diabetes care innovations toward the Chronic Care Model in a middle-income country with a complex set of autonomous public institutions as well as a large private sector.

IMSS faces a major diabetes epidemic affecting the country as a whole and clearly overwhelming the institution, with up to 43% of its beneficiaries seeking care with private or other public providers, with at least 23% of them failing to obtain a minimum number of consultations and 64% failing to receive quality care. While diabetes affects women and younger age groups disproportionately, IMSS does not have a clear strategy to address this situation and has been unable to implement risk targeting. The most acute diabetes care bottlenecks are related to improving early diagnosis and quality of care, particularly ensuring integral care supported by multidisciplinary professional teams.

Innovation should balance the dual challenge of increasing horizontal diabetes care coverage for persons not currently accessing care and vertical scale-up of quality care innovations to improve effectiveness. We found that the costs of scaling-up insulin treatment and establishing interdisciplinary teams are by far the greatest in the set of innovations to implement the Chronic Care Model for diabetes. Scaling-up innovations would imply trebling current expenditure allocated to quality improvements, while reducing horizontal access barriers significantly would imply only increasing what is currently provided to enhance quality by only 43%. Considering just the cost of innovations, it would therefore seem that improving horizontal coverage by itself would be more cost-effective than improving quality of care with the current coverage restrictions. However, when the budgetary impact of innovations is considered in the context of total diabetes care costs, it is clear that the greatest financial impact would be borne by treating a greater number of persons living with diabetes at current standards of care. These trade-offs have to be addressed through a national policy that ensures cross-institutional coverage regardless of affiliation while placing incentives on scaling-up quality of care innovation.

IMSS physicians and leaders are keenly aware of the threats that diabetes poses to the institution and are motivated toward innovation through vertically driven programs and a willingness for training. Yet a high degree of centralization; absence of performance incentives; and high workload, time constraints, and training limitations inhibit performance and hamper innovation.

Innovation also faces barriers in the external context as evidenced by the governance of the response to chronic diseases increasingly affecting the country, the expectations held by beneficiaries living with diabetes, and difficulty to address the budgetary impact of diabetes. The current governance of IMSS depends on a narrow set of actors from industry and labor that fail to represent the vast majority of beneficiaries and are focused on administrative decisions aiming to reconcile narrow political interests rather than focusing on the beneficiary's right to health [29].

The range of expectations held by beneficiaries regarding the institutional response focus on the procurement of medicines and on the passive acceptance of institutional limitations, perceptions that are supported on the ready availability of alternative sources of care and on a focus by IMSS itself on addressing supply of consultations and oral medications rather than on promoting beneficiary empowerment.

The current budgetary impact of diabetes care is around 14% of the sickness and maternity insurance and needs to be taken up to 22% if access and quality of care is to be significantly improved. Yet IMSS financing is characterized by funding shortages given it depends on contributions by employers, employees and the government which are tied to affiliation, itself stagnant in the context of a slow-growing formal private sector.

Recommendations

Given that the most costly and challenging diabetes care interventions are those related to human resources and insulin, reforms should be developed with universities, professional associations, and trade unions as well as with the pharmaceutical industry to ensure breakthroughs in new professional and technical profiles and more efficient pharmaceutical production and distribution. These strategies should be firmly supported on digital innovation capable of drastically reducing treatment costs while improving adherence, quality monitoring, and evaluation. Reforms should focus on efficiency, quality, and equity through a national diabetes care policy capable of empowering persons living with the disease regardless of institutional affiliation and providing cross-institutional technical support and monitoring platforms. Such a policy should also integrate financing through a national diabetes care fund to provide performance incentives and ensure continuity of quality care for persons cycling through the formal and informal economy. Public private collaboration should also be supported through legal and normative changes to enable competition and promote collaboration. Other countries have already experimented successfully with such national disease-oriented policies, with Germany as a case in point given that its social insurance institutions were the basis on which IMSS was established in Mexico [30].

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Clinical Inertia and Diabetes Outcomes

26

Joel Rodriguez-Saldana

Introduction

Health care delivery or medications are not the only possible influences on diabetes control [1, 2]. Patients and physicians' factors and the organization and process of health care interact by need and determine the outcomes. Clinical inertia and patient adherence are two main deterrents of the effectiveness in patient-provider encounters. Awareness, prevention, and tailored interventions to reduce their impact are essential to achieve the goals and improve the quality of diabetes management.

Clinical Inertia

Resistance to accept and implement effective innovations has always been characteristic of every human endeavor, and the history of medicine provides many illustrative examples of evidence-based interventions that had to wait years or even decades before acceptance by practitioners. A major challenge of health care is to increase the uptake of evidence-based medicine in "the real world," that is, knowledge translation, "the process of taking evidence from research and applying it in clinical practice" [3]. The history of medicine is plagued by multiple examples about the difficulties and delays to introduce evidence into this "real world" [3]. Despite the development of new medications, a significant proportion of people with type 1 and type 2 diabetes fail to achieve glycemic goals [4]. One of the main goals of clinical practice guidelines (CPG) is to accelerate the introduction of medical innovations, but implementation and compliance by physicians is still limited and challenged. Clinical inertia is one of the main causes.

Definitions and Evolution

Clinical inertia as an entity was recently described, albeit examples of noncompliance with clinical guidelines or failure to intensify medical treatment have been recognized many years ago. In 1998, for example, Frolkis and colleagues published the results of a chart review of 225 patients admitted to a coronary care unit, in which they showed that despite the wide availability of guidelines for the detection, evaluation and treatment of hyperlipidemia, and the results of major clinical trials of primary and secondary prevention of coronary heart disease, physicians were poorly compliant, even in patients at high risk [5]. Implementation of clinical guidelines and putting evidence-based medicine at work is still far from accomplished [5–8].

Origins and Definition

The term "clinical inertia" was coined by Curtis Cook and colleagues in 1999 to describe the effectiveness of a structured program to improve glycemic control and the importance of self-examination of performance to overcome clinical inertia in 698 African–American patients with type 2 diabetes from Atlanta [9]. Recognizing its importance, the authors of this study established and measured a quality improvement program with increased emphasis on intensification of therapy, along with perceived barriers to advance treatment [9]. Two years later, they authored the landmark review about clinical inertia, which they defined as "the inability of physicians to achieve the goals of treatment after repeated visits," "the recognition of the problem but failure to act," or more specifically as the "failure of health care pro-

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viders to initiate or intensify therapy when indicated" [10]. Recent definitions describe clinical inertia as "an office visit at which no therapeutic move was made to achieve the goals of treatment" [11] or as "failure to treat to target or prescribing that is not concordant with clinical guidelines" [11], with the additional claim that clinical inertia could be "a clinical safeguard for the drug intensive style of medicine fueled by current medical literature and pharmaceutical companies, in the best benefit of patients to adopt less aggressive and also less risky and costly approaches" [12]. Finally, Fraenkel and colleagues defined clinical inertia as "the preference to maintain the status quo, a barrier to implement treat to target protocols in patients with chronic diseases" [13].

The influence of clinical inertia on the negative results of patient management has been documented worldwide in the treatment of a variety of diseases and disciplines, starting with diabetes and including hypertension [14–19], dyslipidemia [20, 21], depression [22], osteoporosis [23], hepatic encephalopathy [24], geriatrics [25, 26], kidney transplantation [27], valvular heart disease [28], dentistry [29], osteoarthritis [30], and chronic obstructive pulmonary disease [31].

The Impact of Clinical Inertia in Diabetes Management

Clinical inertia was originally described in diabetes outpatient management, but it has also been reported in hospitalized patients. Table 26.1 presents a summary of studies published from 1999 to 2021 by a Pubmed search under the terms "Clinical Inertia and Diabetes" and "Failure to Intensify Diabetes Therapy" [9, 32–74].

Table 26.1 Studies about clinical inertia and diabetes

Year	Country and reference	Patients	Type of study or intervention	Results
1999	USA [9]	698 African–American patients with type 2 diabetes	Observational study: self-report of patients with intensified therapy; barriers to advance treatment	Average reduction in HbA1c of 1.4%; progressive improvement in the percentage of patients achieving HbA1c targets; 57% at goal in 5 years
2000	USA [32]	4523 patients with HbA1c results, 2892 with at least one follow-up test	Assessment of diabetes care using pharmacy and laboratory data from nine medical groups to determine dispensing patterns and changes of therapy based on HbA1c results	Despite having HbA1c levels above 8.0%, most patients had no changes in therapy. Inadequate follow-up was documented in more than 60% of patients. The effect of changes in therapy on subsequent HbA1c results could not be assessed.
2003	USA [33]	570 patients with type 2 diabetes receiving metformin in addition to sulfonylureas	Retrospective observational study Pace and patterns of therapeutic failure and clinical responses	HbA1c levels inexorably rise before clinicians react: patients spent months at HbA1c levels above 8.0%, and glucose lowering actions were only established when HbA1c levels were 9.0% or higher. Hyperglycemic peaks preceded changes in therapy.
2004	USA [34]	7208 complete courses of non-pharmacologic or oral antidiabetics	Retrospective observational study Cumulative glycemic burden: months at HbA1c levels above 8.0% or below 7.0%	The average patient accumulated nearly 5 years of excess glycemic burden above 8.0% from diagnosis until starting insulin and 10 years of excess glycemic burden above 7.0%.
2004	USA [35]	598 adults with type 2 diabetes receiving primary care in an academic medical center	Prospective observational study Failure to achieve treatment goals for HbA1c, systolic blood pressure (SBP) or low density cholesterol (LDL) after 1 year	Delays and low rates of intensification for every treatment goal: 51% of patients with high HbA1c, 30% of patients with high SBP and 30% of patients with high LDL had increases in regimes. A decline in the proportion of patients above the LDL after 1 year, not for HbA1c or blood pressure
2005	USA [36]	1765 adult patients with type 1 or type 2 diabetes from 27 primary care and 17 diabetes or endocrinology clinics	Retrospective observational study Measurement and control of HbA1c, blood pressure, cholesterol and corresponding medical regimen changes	High annual testing rates for HbA1c, blood pressure, and total cholesterol (97.7%, 96.6%, and 87.6%, respectively) Patients at goal for HbA1c: 34.0%, for blood pressure: 33.0%, for lipoproteins: 65.1%, for total cholesterol: 46.1%, for LDL cholesterol Only 10% of the patients met the recommended goals for all three risk factors. Lack of intensification was equal for patients with type 1 and type 2 diabetes.

Table 26.1 (continued)

Year	Country and reference	Patients	Type of study or intervention	Results
2005	Canada [37]	591 patients receiving specialist care and 1911 receiving primary care	Retrospective observational study Differences in clinical inertia between specialists and primary care physicians	45.1% of patients receiving specialist care versus 37.4% of patients receiving primary care had drug intensifications ($P = 0.009$), attributed to more frequent use of insulin among specialists High prevalence of clinical inertia in both groups
2005	USA [38]	23,291 patients with diabetes from 13 Department of Veterans Affairs hospitals	Retrospective observational study Developing a valid quality measure to identify clinical inertia and its consequences on glycemic control	Despite 39% of patients having an initial HbA1c level above 8.0%, increases of antidiabetic medications occurred at only 9.8% of visits. Patients receiving more intensive therapy had greater improvements in control.
2005	USA [39]	438 African American patients in primary care and 2157 patients from a specialty clinic by endocrinologists	Longitudinal observational study	Average A1c in the medical clinic: 8.6%, in the diabetes clinic: 7.7% ($P < 0.0001$) Lower number of drugs and rates of intensification occurred in the medical clinic, but intensification at both sites was associated with improvements in A1c. Patients from the medical clinic had worse glycemic control, were less likely to use insulin and to have their therapy intensified if glucose levels were above target.
2006	Australia [40]	531 patients with type 2 diabetes from an urban clinic	Longitudinal observational study Baseline assessment and 5 annual follow-up visits Assess effectiveness of management of type 2 diabetes	Low rates of intensification: after 8.1 years follow-up, 18% of patients progressed from diet to oral antidiabetics (OAD) 9% progressed from OAD to insulin Median HbA1c levels to start OAD or insulin were 7.7% and 9.4%.
2006	USA [41]	345 internal medicine residents receiving computerized reminders about patient-specific recommendations; feedback on performance	Behaviors when glucose was above 150 mg/dL were classified as "did nothing," "did anything," or "did enough" to describe clinical inertia or two levels of intensification	At baseline, residents "did nothing" in 65% of the visits, and "did anything" or "did enough" in 35% of visits After 3 years, 52% "did anything" and 30% "did enough" Active interventions were followed by significant increases in trends to intensify therapy during visits. Health care behavior improved more in the feedback intervention groups than in control groups. Greatest improvements in the first year, decreased afterwards.
2006	USA [42]	Random sample of 5% of 1812 hospital records with a discharge diagnosis of hyperglycemia	Observational study magnitude of clinical inertia in hospital management of diabetes	Despite a diagnosis of diabetes in 96% of patients at admission, daily notes mentioned diabetes in 62% of cases and 60% of discharge notes; only 20% of discharges included diabetes follow-up 86% of patients had bedside glucose measurements, but only 52% had documented assessment of glucose severity. Despite a high frequency of hyperglycemia (71%), only 34% of patients had changes in therapy

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Table 26.1 (continued)

Year	Country and reference	Patients	Type of study or intervention	Results
2006	USA [43]	253,238 patients with hypertension, dyslipidemia, and diabetes	Retrospective observational study	64% of patients experienced modifications for poorly controlled systolic blood pressure, 71% for poorly controlled diastolic blood pressure, 56% for poorly controlled LDL cholesterol, and 66% for poorly controlled A1c. Intensification included increases in the number of drug classes and increased dosage 3–4% of patients with high A1c values achieved control without changes in therapy, Patients' preferences and adherence were not measured,
2007	USA [44]	2065 patients with type 2 diabetes newly started on antidiabetics and followed 3 or more years	Prospective observational study Initial medication adherence and regimen intensification	Baseline medication adherence: 79.8 ± 19.3% By comparison to patients in the highest quartile of adherence, patients in the lowest quartile were significantly less likely to have increases in regime within 1 year of their first elevated A1c. Patients in the highest adherence quartile had 53% greatest odd of medication intensification.
2007	USA [45]	Patients with type 2 diabetes and 211 primary care visits	Cross-sectional observational study Competing demands to changes in antidiabetic medications Intervals of return appointments in patients with high HbA1c levels	Each additional patient concern was associated with a 49% reduction in the likelihood of change in medication, independent of the length of the visit and the most recent level of HbA1c. For each additional increase in HbA1c, the time to the next scheduled appointment decreased 8.6 days. The concept of clinical inertia is limited and does not fully characterize the complexity of primary care encounters.
2008	USA [46]	254 patients with type 2 diabetes	Prospective observational study Visit-based factors associated with intensification of antihypertensive medications in adults with diabetes	Primary care providers intensified antihypertensive treatment in only 13% of visits in which blood pressure was high Higher systolic and diastolic blood pressures were important predictors of intensification. Factors associated with failure to intensify treatment: capillary glucose >150 mg/dL, coronary heart disease, or comanagement by a cardiologist
2008	USA [47]	105 patients with diabetes hospitalized for cardiothoracic surgery	Retrospective observational study Barriers preventing appropriate glycemic control in an academic center	Only six patients (5.7%) had adequate glucose control, 99 (94.3%) required intervention. 30 barriers to achieve glycemic control identified, including "therapeutic reluctance," inappropriate titration of medication, lack of basal insulin, lack of weekend staff trained in diabetes management, use of sliding scale, prescription of inappropriate medications, knowledge deficits of the staff for weekends, and omission to restart outpatient diabetes medications
2009	USA [48]	1718 patients discharged from 37 academic medical centers	Retrospective observational study Contemporary management of hyperglycemia	Wide variations in hospital performance of recommended hospital diabetes care, including A1c and glucose measurement Median glucose significantly lower for patients in intensive care units compared to other areas On the third day of admission, only 25% of patients had 6:00 AM glucose. ≤110 mg/dL 50% of patients had ≥1 glucose measurement ≥180 mg/dL on days 2 and 3 severe hypoglycemia occurred in 2.8% of all patient days

Table 26.1 (continued)

Year	Country and reference	Patients	Type of study or intervention	Results
2009	Netherlands [49]	1283 patients from 30 general practices	Randomized controlled trial on the implementation of a locally adapted diabetes guideline	Percentage of patients with poor diabetes or lipid control who did not receive treatment intensification in the intervention and control group: 90% and 45%, respectively. Clinical inertia was higher in patients above target in blood pressure (72.7% vs. 63.3%). Clinical inertia was less common when nurses participated in the management. In both study groups, cholesterol decreased significantly more in patients receiving treatment intensification.
2010	Canada [50]	379 type 2 patients treated with insulin with and without oral antidiabetics	Survey of 109 family physicians including HbA1c target levels and perceived barriers to insulin initiation and intensification	Mean time from diagnosis of diabetes to insulin initiation: 9.2 years Mean HbA1c values before insulin initiation at visit 1: 9.5%, 8.1% at visit 2 and 7.9% at visit 3 20% of patients at visit three continued with HbA1c above 9.0%
2011	USA [51]	10,743 patients with newly diagnosed type 2 diabetes from an electronic medical record database	Retrospective observational study	Older patients had higher baseline HbA1c values. 59% of younger patients at 2 year follow-up received oral antidiabetics (OAD) compared with 44% in older patients. Median time between diagnosis and start treatment with OAD for younger patients: 350 days; more than 2 years for older patients
2012	France [52]	17,493 patients with type 2 diabetes receiving oral antidiabetics	Retrospective observational study Current procedures to intensify hypoglycemic treatment in general practice according with clinical guidelines	18% of patients required treatment intensification Treatment intensification after second HbA1c: immediately in 39% of patients, within 6 months in 13%, within 6 months in 39% and within 1 year in 59% Treatment intensification was less likely in older patients, and more likely at higher HbA1c levels.
2012	USA [53]	1359 patients from a veterans affairs hospital	Retrospective observational study Effect of hospital admission on the medical treatment of poorly controlled diabetes	Of 2015 admissions, 454 had some change in diabetes medications at discharge (22.4%). Higher preadmission HbA1c levels, higher mean glucose at admission, inpatient hypoglycemia, and use of insulin were associated with greater odds of change in therapy. Clinical inertia occurred in 656 admissions (32%), with no change of therapy, no documentation of HbA1c 2 months after discharge, and no follow-up appointment within 1 month of discharge.
2012	USA [54]	770 patients with type 2 diabetes	Survey of 508 primary care physicians by internet Relevant clinical information and reasons about absence of treatment in older patients	Reasons to omit pharmacologic treatment: use of diet and exercise (57.5%), mild hyperglycemia (23.8%), patient's concerns (13.4%), specific concerns about antidiabetics (3.0%), and comorbidities and polypharmacy (2.3%)
2012	USA [55]	83 primary care physicians	Cross-sectional study Structured interviews Providers perceptions about the importance to initiate insulin therapy, factors and barriers affecting this decision	80% of PCPs endorsed glycemic targets. 54% individualized targets based on age, life expectancy, comorbidities, self-management capacity, and willingness 64% reported that patients were resistant to new oral or insulin therapies because of fears about them 80% cited patients' nonadherence would dissuade them from initiating insulin 64% cited patients' resistance as a barrier to initiate insulin 43% cited problems of patient self-management

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Table 26.1 (continued)

Year	Country and reference	Patients	Type of study or intervention	Results
2013	Spain [56]	2783 patients with type 2 diabetes from primary care centers	Cross-sectional observational study	35.8% of patients had HbA1c levels above 7.0% Intensification of therapy occurred in 66.8%, including increase in dose (40.5%), addition of oral antidiabetics (45.8%), and addition of insulin (3.7%). Clinical inertia was established in 33.2% of patients and diminished along with complexity of therapy and with HbA1c increase. Clinical inertia decreased 47% for each unit of increase in HbA1c
2013	UK [57]	81,573 patients with type 2 diabetes from a national database	Retrospective observational study Time to treatment intensification in patients receiving one, two or three oral antidiabetics (OADs) and associated levels of glycemic control	Median time from HbA1c above goals (≥7.0, ≥7.5, or ≥8.0%) to intensification with an additional OAD: 2.9, 1.9, or 1.6 years, respectively, for patients taking one OAD, and >7.2, >7.2 and >6.9 years for those taking one, two, or, three OADs Mean HbA1c at intensification with another OAD or insulin for patients taking one, two, or three OADs: 8.7, 9.1 and 9.7% Probability of intensification in patients with poor glycemic control taking one, two, or three OADs at the end of follow-up with another OAD: 21.1–43.6%; with insulin: 5.1–12.0%
2014	UK, Spain, Brazil, India, Japan, USA [58]	652 patients with type 2 diabetes and 337 physicians	Cross-sectional study; 20-min online survey Opinions related to clinical inertia from patients and physicians' perspectives Perceptions and expectations about diagnosis, treatment, diabetes complications and therapeutic escalation	Important discrepancies in terms of patient and physician perceptions Physicians have low expectations for their patients. Patients have. at best, a rudimentary understanding of the risks of complications and the importance of control. Only 25% were reported to be worried about developing diabetes complications; the rest were either not concerned or thought the risk was remote. A small proportion believe that lifestyle changes are important; only 37% acknowledge that this is a treatment modality. The majority do not intend to adhere to treatment. Impairments in communication are at the heart of clinical inertia.
2014	Bahrain [59]	334 patients from a diabetes outpatient clinic	Retrospective observational study Association between clinical inertia with simpler interventions and outcomes	Greater treatment intensification for high HbA1c than for high blood pressure or LDL Clinical inertia for hyperglycemia: 29%, hypertension: 68%, high LDL: 80% Omission to increase oral antidiabetics or insulin occurred in 29% of medical visits Omission to increase antihypertensives occurred in 67.5% of medical visits Omission to increase lipid lowering therapy occurred in 79.7% of medical visits Clinical inertia is greater for blood pressure and lipid control than for hyperglycemia

Table 26.1 (continued)

Year	Country and reference	Patients	Type of study or intervention	Results
2014	Spain [60]	2971 patients with type 2 diabetes, 1416 controlled (A1c <7.0%) and 1555 not controlled (A1c ≥7.0%)	Retrospective, cross-sectional observational study	Prevalence of partial clinical inertia (PCI) in some medical visits was 52.5%. Prevalence of total clinical inertia (TCI), absence of intensification of therapy in all visits despite A1c ≥7.0% was 12.8% PCI was lower in patients controlled and associated with sedentary lifestyle, hypertension, and a higher prevalence of vascular complications,
2015	UK [61]	20 healthcare providers in general practice	Interviews with 20 providers, 19 physicians, and 1 nurse Ten providers worked in general practices with high scores for quality and outcomes framework (QOF) targets 10 providers from lower scoring practices	Most of the people interviewed were unaware of the term "clinical inertia" or unclear about its meaning. Interviewees from both lower and higher scoring practices were willing to acknowledge limitations in achievements related to glycemic control and a degree of responsibility. Participants had inaccurate perceptions about levels of achievement in their primary care centers and sought to lessen their own accountability by highlighting patient and system barriers. Addressing clinical inertia was not seen straightforward, as result of a complex and cumulative pattern of barriers at the provider, patient, and system level
2015	Croatia [62]	10,275 patients with diabetes	National, cross-sectional, observational study Rate of clinical inertia to treat diabetes in primary care; association of patient, physician, and health setting factors	Clinical inertia occurred in 57.7% of clinical encounters. Mean clinical inertia by practitioner was 55.6%; 9% were clinically inert with all patients. Clinical inertia was associated with increases in HbA1c. Patient and physician characteristics associated with clinical inertia: fasting blood glucose, hypertension, high triglycerides, unhealthy dietary habits, chronic comorbidities, number of patients under care, number of daily medical visits, and initiation of oral antidiabetics HbA1c levels had the highest association with clinical inertia; patients with worse glycemic control were more likely to experience it.
2015	USA [63]	75,000 patients with type 2 diabetes from a managed care claims database (IMPACT©)	Prevalence and predictors of clinical inertia based on personalized goals Three HbA1c targets to identify patients above targets during the index period; clinical inertia was defined as no intensification of treatment during the response period	Regardless of HbA1c target, 70% of the patients experienced clinical inertia over 6 months and remained above 50% up to 3.5 years later. Time to intensification by addition of an oral antidiabetic, insulin or a GLP-1 receptor agonist ranged from 50.5 to 59.0 days at 6 months and from 702 to 738 days at follow-up. During the first 6 months, 20% of patients were prescribed an oral antidiabetic, 5.3% received insulin, and 2.0 a GLP-1 analog predictors of intensification: point of service insurance, mental illness, a visit to an endocrinologist, or higher HbA1c level. Intensification was less likely in older patients, patients taking more than one antidiabetic during 6 months, or recent HbA1c measurement above target.

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Table 26.1 (continued)

Year	Country and reference	Patients	Type of study or intervention	Results
2016	UK [64]	11,696 patients with type 2 diabetes from a clinical practice research database	Retrospective observational study Prevalence of clinical inertia in patients treated with basal insulin	Basal insulin was started in all patients at a mean ± SD HbA1c of 9.7 ± 2.0% 80.3% of patients were receiving ≥2 oral antidiabetics at the start of insulin. 36.5% had intensification of treatment Median time to intensification: 3.7 years Delay to intensify was associated with increasing age, duration of diabetes, use of oral antidiabetics, and Charlson comorbidity index score. 32.1% of patients with HbA1c ≥7.5% suspended basal insulin
2016	Finland [65]	1075 adult patients with type 1 diabetes from a regional electronic patient database and medical records	Retrospective observational study To investigate if the targets established in the guidelines for patients with type 1 diabetes are achieved in medical practice	Despite one of the highest worldwide prevalence of type 1 diabetes (0.8%), only 19% of patients reached a HbA1c target of <7.0% and 45% had LDL levels below 100 mg/dL Overall, 13–16% of patients younger than 60 and 26% of patients older than 60 years achieved targets of glycemic control.
2016	Thailand [66]	98 patients with type 2 diabetes and mean HbA1c 10.3%	Retrospective observational study Effects of clinical inertia on glycemic control and diabetes related complications	Prevalence of clinical inertia: 68.4% Mean decrease of HbA1c at 6 months: Clinical inertia group: 0.82 ± 1.5% Non-inertia group: 3.02 ± 1.8% After 4 years: 1.46 ± 1.85% and 3.04 ± 1.76% Clinical inertia was associated with a shorter median time to progression and a higher incidence of diabetic retinopathy Adjusted incidence rate ratio of diabetic retinopathy in the clinical inertia group: 4.92
2017	Belgium [67]	578 insulin-naive patients with type 2 diabetes	Retrospective cohort study, 8-year analysis, 1.2 years follow-up Clinical inertia defined as equivalent to prolonged inaction (PI): no change in treatment with an A1c level > 7.0% for a 12-month minimum	Prevalence of clinical inertia or PI: 59% Associated factors: Moderate to severe chronic kidney disease (CKD) Less-frequent A1c measurement Lower A1c levels Less additional medications Physicians lag behind clinical guidelines: the "real trigger" for action is not an A1c level of 7.0%, intensification occurs above 7.0% or even at 8.0% Except for CKD, severe comorbidity does not impede adjustment in hypoglycemic treatment. Intensive follow-up at the process level is associated with intensive treatment adjustments.
2018	France [68]	6045 patients ≥18 years with type 2 diabetes either simultaneously or sequentially treated with two OADs, GLP-1 receptor agonists or basal insulin	Retrospective analysis of a database of commercial claims Clinical and economic outcomes in patients with uncontrolled type 2 diabetes initiating two OADs, GLP-1 agonists or basal insulin 1-year follow-up	Despite A1c lowering following treatment initiation, many patients do not achieve A1c goals, suggesting a need for earlier or more intensive treatment. The percentage of patients with A1c >7.0% 4 years after initiation of a new class of antihyperglycemic medication ranged from 48% with OADs to 74% in patients initiating basal insulin. Baseline A1c was highest in patients receiving basal-insulin as second drug (10.1%) At the last follow-up measurement, 47.5% of patients initiating OADs, 41.1% of patients initiating GLP-1 agonists, and 32-0.6% of patients initiating basal insulin had A1c levels <7.0%.

Table 26.1 (continued)

Year	Country and reference	Patients	Type of study or intervention	Results
2018	USA [69]	6597 patients with type 2 diabetes who started basal insulin following OADs and had at least one valid HbA1c result 90 days before and 720 days basal insulin initiation	Retrospective analysis of a database of commercial claims Probability of achieving glycemic control over 24 months after baseline insulin initiation in patients with type 2 diabetes	Average HbA1c at basal insulin initiation: 9.1%, 1.5% decrease in the first 6 months after, with no further reduction Rapid decrease in the probability of reaching glycemic control in the first year and remained low in the second year 38% of patients reached HbA1c <7.0% in the first year, 8.0% in the second year
2018	USA [70]	7389 patients with type 2 diabetes and an A1c value ≥7.0% despite a stable regimen of two OADs for at least 6 months	Retrospective analysis of an electronic health record system	62.9% of patients had no evidence of treatment intensification, including 71.7% of patients with A1c 7.0–7.9%, 53.3% of patients with A1c 8.8.9% and 44.4% of patients with A1c ≥9.0% Physicians do not respond quickly enough to poor glycemic control, even in patients with A1c levels far exceeding typical treatment targets
2018	Germany [71]	4576 patients with type 2 diabetes not achieving glycemic control (HbA1c >7.0%) with dipeptidyl peptidase-4 inhibitors (DPP-4i) and sodium/glucose cotransporter 2 inhibitors (SGLT-2i)	Retrospective observational study	Mean time on poor glycemic control until most recent visit was: 12.6 months with HbA1c >7.0% 9.9 month with HbA1c >7.5% 8.4 months with HbA1c >8.0% Even with the use of new oral antidiabetics, a substantial proportion of patients do not achieve glycemic control
2019	United States [72]	7389 patients with type 2 diabetes and an A1c value ≥7.0% despite a stable regimen of two OADs for at least 6 months	Follow-up retrospective analysis of an electronic health record system*	Probability of achieving an HbA1c goal of 7.0% At a baseline level of 7.0–7.9% with addition of: Oral antidiabetics: 57.3% GLP-1 agonists: 56.7% At a baseline level of 8.0–8.9% with the addition of: Oral antidiabetics: 31.9% Insulin: 30.6% At a baseline level ≥9.0% with the addition of: GLP-1 agonists: 53.0% Insulin: 43.5% Goal attainment by type of intensification was more likely in patients with HbA1c levels ≥9.0%
2020	Malaysia [73]	7646 patients with type 2 diabetes from a national diabetes registry	Retrospective observational study	Median time to treatment intensification: 15.5 months, 19 months, and 27.8 months under the best, average, and worst-case scenarios Total proportion of patients with treatment intensification: 45.4% of which 34.6 occurred only after 1 year Patients treated with more antidiabetics were less likely to have treatment intensification
2021	United Kingdom [74]	254,925 people with incident type 2 diabetes, dyslipidemia (66%) and hypertension (66%) from a primary care database	Retrospective observational study	Significant delay in initiating cardioprotective therapies irrespective of atherosclerotic vascular disease risk status across all age groups resulting in poor risk factor control at 2 years follow-up Median number of months to initiation of therapy for persons with dyslipidemia: 20.4 Median number of months to initiation of therapy for persons with hypertension: 28.1

*Type of study

These studies confirm the magnitude, the negative outcomes, and the benefits of interventions to reduce the effect of clinical inertia in diabetes management. The following conclusions can be made:

1. Clinical inertia for all diabetes goals including glucose, blood pressure, and lipoprotein profile is high and equally remarkable in patients with type 1 and type 2 diabetes: 19% in type 1 diabetes; 33–70% for HbA1, 30% for hypertension, and 30% for low-density lipoprotein (LDL) cholesterol in type 2 diabetes.
2. The glucocentric approach prevails: treatment intensification is more likely for high HbA1c than for hypertension or high LDL cholesterol.
3. Lack of glycemic control occurs at every clinical setting: outpatient, inpatient, medical and surgical.
4. Physicians have low levels of awareness about clinical inertia.
5. Even at levels of high risk, the response of clinicians to clinical inertia is insufficient representing up to 5 years of excess glycemic burden.
6. Rates of treatment intensification are low (less than 10.0%) and slow (up to 5 years).
7. Rates to initiate every therapeutic modality, including newer therapeutic classes, are low and slow, with insulin at the top (up to 9.2 years).
8. After hospital discharge, high rates of hyperglycemia (64%), persistent hyperglycemia (50%), and low rates of diabetes follow-up (20–22%) have been documented.
9. Clinical inertia is also associated with low patient adherence, disregard of glycemia, patient concerns, comorbidity and polypharmacy.
10. Intensification of therapy improves metabolic control, reducing HbA1c, blood pressure, and LDL cholesterol levels.

Factors Associated with Clinical Inertia

For factors associated with clinical inertia, in their classical review, Phillips and colleagues identified three groups of factors as the main causes of clinical inertia: (1) overestimation of care provided, physicians consider that patients are improving despite lack of change in clinical results; (2) subjective or "soft reasons" to avoid intensification of therapy ("the patient is improving"); and (3) lack of education, training, and practice organization focused on achieving therapeutic goals [10]. The third group of factors include challenges to implement clinical guidelines, such as ignorance about their existence, lack of compliance, denial, or frank rejection by physicians [5, 75, 76]. Beyond glycemic control, clinical inertia involves all the aspects of diabetes management: Worrall and colleagues showed that 53% of patients had HbA1c measurements done in the previous year and that the average number of procedures and tests conducted by family physicians in Canada was 5.9 from 11 recommendations by the Canadian Diabetes Association [75]. Table 26.2 summarizes factors associated with clinical inertia [77–85]:

Table 26.2 Factors contributing to clinical inertia

Author and reference	Description
Phillips et al. [10]	Overestimation of the care provided "Soft reasons" to avoid intensification Lack of training
Fantini et al. [6]	Organization "arrangements": individual versus in-group practice Patient characteristics: older age, comorbidities Location of practice: rural versus urban
Barth et al. [8]	Age of physicians: older clinicians more frequently work in individual practice and rely on experience; younger clinicians more inclined to accept collaborative, team-based medicine, protocols, and clinical guidelines
O'Connor et al. [77]	Physician factors: failure to initiate and titrate treatment until goals are achieved; failure to identify and manage comorbidities; ineffective clinical encounters; insufficient time; reactive, instead of proactive, care Patient factors: denial or belief that the disease is not dangerous, low health literacy, cost and amount of medications, side effects, poor communication or distrust in physicians, depression System factors: absence of clinical guidelines or disease registries, planning deficiencies, absence of outreach, support and team approach, poor communication
Reach [78, 79]	Discrepancy between the technical rationality of evidence-based medicine and the modes of reasoning of physicians "in real life" "Clinical myopia": failure to give preference to the benefits of treatment intensification
Miles [80, 81]	"Fallacious reasoning and cognitive bias": a conscious decision to withhold or omit the use of evidence-based medicine
Safford et al. [82]	Appropriate inaction; potential appropriate decisions resulting from patients' factors: lack of adherence, psychological or physical stress, lack of resources
Aujoulat et al. [83]	Providers' knowledge of and attitudes toward evidence-based guidelines: Insufficient knowledge, disagreement or distrust, lack of applicability Providers' clinical judgment and experience within specific situations Sociodemographic characteristics and medical history of patients, values, comorbidities, polypharmacy, concerns, and reluctance Providers' awareness of patients' attitudes, behaviors, preferences, adherence, literacy, and empowerment Providers' ability to make the appropriate decision within a given clinical and organizational context: reluctance or difficulty to change, clinical uncertainty, limited time, absence of multidisciplinary or team-based care

Table 26.2 (continued)

Author and reference	Description
Strain et al. [84]	Physician factors: overrating the quality of care provided, underestimating the number of patients who are not in target, use of soft excuses to avoid intensification, lack of time, blaming patients' noncompliance, paternalistic approach, knowledge or training to manage multiple chronic diseases, lack of clarity of clinical guidelines Systemic contributors: traditional clinical guidelines focused on goal-setting pathology management disregarding the importance of communication between patient, physicians and multidisciplinary teams (if available); physicians working in isolation within the health system; time constraints, delays Patient factors: non-adherence; socioeconomic factors; lack of understanding and engagement with the treatment
Kunthi et al. [85]	Clinician-level barriers: limited awareness of clinical inertia; clinicians' overestimation of their quality of care and adherence with guidelines Patient-level barriers: lack of health education, disbelief in the efficacy of therapy, concerns about effects of therapy on quality of life, fear of side effects, lack of confidence to adhere to complex regimes

Clinical Inertia in Defense of Patients

Clinical inertia, in defense of patients in counterpart to its negative implications, has also been described as a clinical safeguard, based on the results from clinical trials showing absence of clinical benefits on cardiovascular outcomes with tight glycemic control in patients with type 2 diabetes, and increases in all-cause mortality, hypoglycemia, and weight gain, particularly patients with frailty and the elderly. Comorbidities and competing health, personal, and social factors are common in patients from every age group, and interventions to correct them are essential components of management. A retrospective analysis to examine physician and patient characteristics showed that nearly all physicians have practiced clinical inertia and that the volume of patients was the most important variable, but patient characteristics including older age, obesity, and comorbidities are stronger predictors, and physicians frequently have to devote their limited time to address other medical problems and to take into account patient's priorities and preferences [76]. At the opposite end of treatment intensification lies the fourth level of prevention, quaternary prevention, originally described by Marc Jamoulle in 1995 [86]. Quaternary prevention is defined as "action taken to identify patients at risk of excessive medical treatment and to protect them from medical interference," which has become an international movement against overmedicalization that has been endorsed and embraced by general physicians and specialists worldwide [86–88]. The principles of hastening to help and doing no harm have to be considered when establishing the relative risks of clinical inertia versus overtreatment in patients with diabetes [85]. The concept of quaternary prevention is all-pervasive; it should be adopted by the diabetes care team and be expressed in every patient-provider contact [88].

Contribution of Clinical Guidelines to Clinical Inertia

One of the main goals of clinical guidelines is guiding physicians to overcome clinical inertia, but reluctance to comply with them is highly prevalent [89]. Clinical guidelines may also contribute to clinical inertia, when they focus on limited aspects, like selecting medications, in disregard of other components of successful treatment like patient education and self-monitoring of blood glucose [90]. Recent guidelines issued by the American College of Physicians (ACP) for glycemic targets in adults with type 2 diabetes addressed these challenges and proposed four guidance statements: (1) personalization of goals for glycemic control, (2) establishing an HbA1c target between 7.0% and 8.0% in most patients, (3) de-intensifying treatment in patients achieving HbA1c levels below 6.5%, and (4) liberalizing control in patients with life expectancy less than years, advancing age or severe comorbidities [91]. While the message conveyed by the revised ACP guidelines is about safety, it has arisen criticism and concern from experts and academia [92, 93]. Arguments against this approach are that while the message conveyed by the American College of Physicians guidelines is one concerning safety, it does little in terms of elaborating on the recommendations concerning an HbA1c target between 7% and 8% [93]. Newer available antidiabetics facilitate glycemic control at lower risk of hypoglycemia, and the concern is that the revised ACP statements may stimulate and validate it [93].

Treatment algorithms cannot be always evidence-based because they are unable to present all the available treatment options [94], but recent guidelines have stressed the importance and, more frequently, the influence and dominance of comorbidities and social determinants of health in the selection and intensification of therapies [95].

Awareness and measurement of clinical inertia is increasing, and it has been shown that it is more important than poor adherence to therapy by patients in the outcomes [96, 97]. It has been also shown that educating physicians is less fruitful than educating patients [98]: Roumie and colleagues, for example, published a study in which 182 providers were randomly assigned to receive several alternatives of education, including online access to the JNC 7 guidelines on prevention, evaluation, and treatment of high blood pressure, and 1341 patients with hypertension received computerized alerts and letters advocating drug adherence and face to face educa-

tion. After 6 months, patients who received education had better hypertension control and lower systolic blood pressure than patients in whom physicians were the ones who received education [98]. Analysis of physicians' responses to computer alerts to comply with the JNC 7 guidelines replicated the list of the "soft reasons" described in the landmark review by Phillips et al., including lack of agreement with the guidelines (5%), patient-based factors (17%), environmental factors (10.5%), lack of knowledge (2%), and soft arguments supporting clinical inertia in 66% ("continue the current medications and I will discuss at the next visit") [98].

Addressing Clinical Inertia

The role of clinical inertia [99] in the poor results to achieve the goals of glycemic control, hypertension, and hypercholesterolemia has been clearly established [100]. Accordingly, several strategies have been proposed to address and modify its negative effects:

1. Raise the awareness: more studies about the epidemiology and consequences of clinical inertia are required to measure its worldwide extent, including individual patient, physician and clinic factors, patient–physician relationship factors, and "complex patient" selection effects including competing health problems and nonadherence [100].
2. Measurement: clinical inertia affects the outcomes and the quality of health care; application of established methods or the development of new measures to quantify its magnitude is essential. Current measures of clinical inertia in diabetes include: (1) percentage of patients having drug therapy intensification at visits above goals of glycemic control [100], (2) proportion of patients with high HbA1c levels after drug intensification [32], and (3) predictive models to establish the probability that an individual visit would result in an increase of antidiabetic medications based on characteristics at that visit including diabetic complications, cardiovascular risk factors, psychiatric or substance abuse disorders, and comorbidities [39]. The complexities and limitations of this method have been addressed by O'Connor, including poor documentation of interventions; use of a normative, instead of a threshold value; placing excessive emphasis on glucose control; and diverting attention from other diabetes quality measures [100].
3. Physician education serves as a key strategy to facilitate intensification of therapy [101]. Targeted interventions to health providers, including (1) enhanced primary care incorporating key features of clinical trials into routine chronic disease care [100, 101]; (2) scheduled, frequent, and carefully planned office visits increased direct contact time with patients [100–102]; (3) electronic medical records to provide real-time decision support to physicians during office visits measure opportunities for intensification and variations by practice and patient characteristics [100–102]; (4) monitoring, prompts, feedback, and decision support for healthcare providers to improve systems [100–102]; (5) continued managerial momentum involving five stages: (a) review the process of diabetes care, (b) identify the highest priority goals and treatment strategies, (c) increase clinical encounters in which clinicians take appropriate action, and (d) tracking progress toward achieving goals, (e) feedback to make patient-care decisions [102]; (6) performance measures to improve care and control costs, including process (accountability) and intermediate outcome items [101, 102]; and (7) incentives and pay for performance [100–102].
4. Effective communication with patients: explanation and risk management in the real world, understanding of the progressive nature of diabetes and the accompanying need to review and adjust treatments [103]. Suitable interventions to promote patient activation, involvement in decision-making and enhance adherence including feedback, education, and support [100–103]. Delivering diabetes self-care and support education and support that patients can understand, according to personal values and preferences [95, 103, 104].

Conclusion

Clinical inertia is a huge problem with dire consequences in the outcomes and the quality of diabetes care. Despite exhaustive efforts to develop evidence-based, unbiased, and feasible clinical practice guidelines, doctors frequently do not follow them. It is the consequence of a discrepancy between the technical rationality of evidence-based medicine and the reasoning of clinical practice in "real life," marked by uncertainty and risk [105]. Overcoming clinical inertia is a big challenge; to address this need, the American Diabetes Association launched a 3-year initiative called Overcoming Therapeutic Inertia (OTI) which includes three phases—Phase 1: Convening Stakeholders, Phase 2: Charting a Course, and Phase 3: Implementing Solutions [106]. The framework of this initiative involves six elements, starting with the dire need to raise the awareness about the magnitude and consequences of clinical inertia, collecting evidence about evidence-based solutions, establishing partnerships, educational interventions, and assessing effectiveness to meet goals [106].

Like other human complex problems, reducing clinical (or therapeutic) inertia requires complex solutions, starting at medical schools, and supported by updated, continuing education and assessment of physicians' performance and

outcomes. Epidemiology, analysis of responsible factors (awareness, attitude, training, organization), and design of interventions about clinical inertia are clearly areas of opportunity to improve one of the crucial aspects in diabetes care.

Multiple Choice Questions

1. Clinical inertia:
   (a) Has been recently described
   (b) Is uncommon
   (c) Is the patient's fault
   (d) **Has been described for decades**
   (e) Is exclusive of primary care
2. Clinical inertia is defined as:
   (a) Promptness to intensify medical treatment
   (b) The trend to align with medical trends
   (c) **Inability to achieve the goals of treatment after repeated visits**
   (d) **Failure to initiate or intensify treatment when indicated**
   (e) **Recognition of a problem but failure to act**
3. Clinical inertia has been reported:
   (a) Only in diabetes management
   (b) In hypertension
   (c) In diabetes and hypertension
   (d) In acute disease care
   (e) **In the management of multiple chronic diseases**
4. The reported prevalence of clinical inertia in the management of diabetes, hypertension, and LDL cholesterol is around:
   (a) 10%
   (b) 20%
   (c) **30%**
   (d) 40%
   (e) 50%
5. Treatment intensification in patients with diabetes may be delayed up to:
   (a) 1 month
   (b) 3 months
   (c) 6 months
   (d) 1 year
   (e) **5 years**
6. Introduction of insulin in diabetes treatment may be delayed up to:
   (a) 1 month
   (b) 3 months
   (c) 1 year
   (d) 5 years
   (e) **More than 9 years**
7. Clinical inertia in patients hospitalized and with diabetes:
   (a) Is nonexistent, quality of diabetes care is optimal in hospitals
   (b) **Is associated with persistent hyperglycemia and low rates of follow-up**
   (c) Is minimal with no appreciable effects on outcomes
   (d) Has been overemphasized
   (e) Has not been investigated
8. Leading factors associated with clinical inertia include
   (a) Overestimation of the care provided
   (b) Subjective reasons to avoid intensification
   (c) Lack of training, practice limitations
   (d) **All of the above**
   (e) None of the above
9. Clinical inertia may be a resource in defense of patients
   (a) **True**
   (b) False
10. Clinical guidelines may contribute to clinical inertia
   (a) **True**
   (b) False

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Patient Adherence: Challenges, Myths, and Realities

27

Joel Rodriguez-Saldana

The missing link in the cycle of clinical drug development is Pharmionics, the study of what the patient does with the drug.

John Urquarth.

Introduction

To achieve the desired results of medical interventions, patients need to keep appointments, take medications, and make lifestyle changes. Their capacity to accept and carry out these tasks is unpredictable; adherence to medical recommendations is highly variable: some people are unable or unwilling to follow all of them, and only a small proportion have high levels of "compliance, adherence or concordance" [1]. Awareness about patient adherence in diabetes is important because it is associated with clinical outcomes and costs: it is estimated that for every 25% increase in medication adherence HbA1c levels decrease by 0.34% [2]. Conversely, nonadherent patients are more likely to require hospitalization and to incur in higher health care costs [2]. Adherence is a crucial link in the physician–patient interaction in chronic disease management. Suboptimal adherence to medications is frequently the main obstacle to the success of drug therapy; it is very common, it is associated with morbidity and mortality, and it is largely neglected and misunderstood [3].

An Evolving Concept

The discordance between medical prescription and patient adherence has been described since ancient times, but finding the right term has been very difficult. In 2012, Vrijens and colleagues described the evolution of the nomenclature defining and describing adherence to medications; from 1961 to 2009, they identified 146 articles and introduced a new term to describe it as "deviations from prescribed treatments." Over five decades, the main used terms were: Adherence, Compliance, Persistence, Concordance, Pharmionics, Therapeutic alliance, Persistency, Patient irregularity, and Pharmacoadherence [3]. As of today, Adherence and Compliance continue to be the preferred terms with opposite implications and are still inaccurate to describe the attitude of patients toward medical recommendations.

Defining Adherence

Over the years, adherence became the most common term, defined "as the extent to which patients take medications as prescribed by health care providers [4]." Traditional terms like "compliance" are based on the assumption that patients are supposed or willing to obey or follow medical orders [4, 5]. These assumptions are unrealistic and continue to produce conflicting differences between patients and physicians. Patients' expectations are personal, unique, and elaborate: they arise from multiple sources including past experiences with physicians; observations and comments from relatives, neighbors, friends and colleagues; public and professional attitudes; and the media [6]. Professional beliefs are also influenced by personal experiences as patients, parents, relatives, observers, professional experience, and personality [6]. Frequently and unfortunately, when patients do not meet physicians' expectations, they are labeled as "noncompliant," implying the moral failure to behave appropriately [7]. The medical concept of compliance is far from reality but still deeply rooted among physicians all over the world, and despite their crucial influence on the outcomes, interventions to improve adherence are not aimed at patients

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[5]. By comparison, terms like concordance, cooperation, agreement, and therapeutic alliance imply a "meeting of minds and perspectives of health providers and patients [3]. At long last the "compliance problem" is getting a new name and with it has created a new view of the patient's role in the doctor–patient relationship [4].

Addressing Nonadherence

Adherence rates are low even among participants in clinical trials, especially for chronic diseases [8]. The design of drug trials have come to recognize the biased and limited scope of compliance and the impact of patient's behavior on statistical power and interpretation of results [5]. Lack of adherence is associated with higher rates of hospital admission, suboptimal clinical outcomes, increased morbidity, mortality, and health care costs [8, 9].

A Brief Story of Adherence

As far back as Hippocrates, physicians were concerned that patients did not follow their advice, and the resulting negative health outcomes increased the authority of physicians' recommendations [10, 11]. Infectious diseases became the first focus of patient's compliance, especially tuberculosis, which was contagious, very frequent, affected people from all socioeconomic levels, and was highly deadly before the advent of antituberculous drugs. The introduction of the first effective antituberculous drugs in the 1940 increased blaming of patients who are unwilling to accept hospitalization to receive extended course of antimicrobials [11].

Drug compliance started to be measured in the prophylaxis against streptococcal infection, and it was shown that the frequency and number of doses was inversely proportional to adherence and effectiveness of therapy [11, 12]. Further trials among children with rheumatic fever showed that penicillin injections were more effective than oral sulfas or penicillin [13, 14]. The importance of adherence to long-term therapies increased with the discovery that blood levels of p-aminosalicylic acid were lower than expected in patients with tuberculosis [15, 16] and that complexity reduced completion of therapy [17].

Social, cultural, and economic factors affecting compliance with treatment were recognized. Scientists from other disciplines began to study the personal, family, and environmental importance of adherence to medical recommendations and to explain "illness behaviors" or "sick roles" beyond the medical perspective [18–20]. Early reports showed that physicians' expectations about patients' willingness to following medical orders were unrealistic [21]. Patients' decision to accept or reject medical recommendations results from multiple factors, including their attitude toward physicians and health, knowledge about risks associated with the disease, and personal approaches to life [22]. Studies in diverse therapeutic areas confirmed these findings: in patients with heart disease, Johannsen and associates showed that education level was associated with disregard of medical advice [23]. In patients receiving antacids, Caron and Roth reported that even in patients admitted to hospitals, most of physicians inaccurately and subjectively overestimate real adherence to treatment and that they are unable to distinguish patients who actually adhere [24]. An early review about the effectiveness of three strategies to detect defaulters: (1) direct interrogation, (2) remaining tablet counting, and (3) measuring drug metabolites showed that doctors' perceptions are related to their "social distance" with patients and reasons for noncompliance included patient's "personality," doctor's attitude, capacity of patients to understand doctor's advice, personal difficulties of patients, and economic capacity to follow medical advice [25]. Explanation, reminders, and persuasion are very important to decrease noncompliance, while authoritarian and threatening attitudes reinforce it [26]. Davis described ten categories of doctor–patient interaction, ranging from mutual antagonism, disagreement, and tension to interactions releasing mutual tensions and arising satisfaction from patients and physicians [27]. Francis and colleagues showed that 24% of pediatric outpatients were dissatisfied with their relationship to their doctors, 42.1% were highly compliant, 38% moderately compliant, and 11.4% totally noncompliant [28]. Empathy, professional attitude, and understanding or concern is associated with compliance, whereas unmet key factors, lack of warmth in the doctor–patient relation, and not receiving explanations about diagnosis and cause of the child's illness were associated with noncompliance [27]. Factors related to lack of adherence in children were almost identical to findings reported in adults [29].

More accurate and sensitive techniques to predict noncompliance were proposed, because methods used in those days were inaccurate, impractical, or alienate patients [30]. Baekeland and Lundwall recognized the importance of dropping out of treatment, its high frequency; identified patients most likely to drop out and factors responsible, personality traits and therapeutic styles, implications and interventions to reduce the risk of dropping out, including patient selection and changes in treatment settings and approaches; and also asked if patients simply abandon treatment or if they abandoned and/or were pushed out of it (if they were invited to drop-out) [31]. Rosenstock reported that compliance was associated with behavioral characteristics, including motivation, "patients' interest and concern" with their health, perceived threats posed by disease, perceived benefits of medical interventions, knowledge of the medical condition, and understanding of expected effects of treatment, including

schedules and doses of medications [32]. He acknowledged that patients do not receive adequate information about treatment because of organization factors, such as long waiting times and distancing attitudes between physicians and patients [32]. Stewart and colleagues asked patients with chronic diseases treated by family physicians in Canada what factors affect the quality of the relationship and if the doctor/patient relationship affected the outcomes, and they found that physicians' factors, including number of health problems and visits and allowing the patient to start the dialogue during visits, were associated, while patients' factors were not [33]. Time and attention to identify comorbidities and continuity in health care would increase physicians' performance [33].

Other reports confirmed the inaccuracy of physicians to predict noncompliance and the need to deal beyond the biomedical aspects of disease, as well as with social and behavioral characteristics of patients. If these factors are not integrated into decision-making, it is unlikely that treatment based exclusively on technical considerations will be effective [34, 35]. Noncompliance is the result of complex interactions of patients and providers, health beliefs, social and behavioral characteristics, the disease or disorder, the complexity of treatment, and organizational strengths and deficiencies; all of them exert strong influences amenable to modification but scarcely studied [36]. In sharp contrast with traditional medical explanations about nonadherence, 40 years ago, it was shown that (1) compliance is not related to income, social class, occupation, or education; (2) physicians are unable to predict patients' willingness or ability to comply; and (3) most of the errors in taking medications are unintentional and related to the complexity and duration of therapy, number of medications, degree and modalities of counseling, and the use of dispensers [36]. Remarkable changes have occurred in philosophical paradigms and related concepts [3].

Compliance, Concordance, or Adherence?

It is essential to find an adequate definition that could at least provide an approximate idea about what is involved when patients respond positively to physicians' recommendations, *when they comply or adhere*. "Compliance" has permeated medical science and implies the existence of a medical-centered model, while "adherence" implies that patients have more autonomy in defining and following medical treatment [37]. Glasgow and Anderson disagreed with this statement and claimed that (1) "compliance and adherence" were counterproductive terms, (2) these approaches are useless when they send the wrong message to patients and health professionals, (3) the multidimensional nature of behaviors lead to adherence, instead of the traditional idea that it is the result of the unitary patient–physician interaction, and (4) there is a dynamic, always changing nature of treatment [38]. They proposed alternative terms such as self-care or "self-management" to describe the cluster of daily behaviors that patients perform to manage their (personal) diabetes [38].

Table 27.1 shows the evolving definitions of compliance, concordance, and adherence [3, 10, 38–46]:

The story of definitions about a persons' behavior in response to "medical orders" shows that: (1) there is still not

Table 27.1 Definitions of compliance, adherence, and concordance

Year	Author(s) and reference	Term	Definition
1976	Haynes [10]	Compliance	The extent in which the patient's behavior in taking medications, following diets, or implementing lifestyle changes coincides with medical or health advice
1982	Dracup and Meleis [39]	Compliance	Extent to which an individual chooses behaviors that coincide with a clinical prescription
1987	Meichenbaum and Turk [40]	Adherence	Degree to which a patient follows instructions and prescriptions of his doctor
1993	Wright EC [41]	Compliance	Different meanings: Medication taking? Changes in diet? Advice on exercise or smoking? Keeping appointments?
1996	Urquart J [42]	Compliance	Extent to which the patients' actual history of drug administration corresponds to the prescribed regimen
1997	Houston-Miller et al. [43]	Compliance with medical recommendations	Extent to which recommendations are followed as defined
2003	World Health Organization [44]	Adherence	Extent to which a person's behavior corresponds with agreed recommendations from a health-care provider.
2005	Balkrishnan [45]	Adherence	Extent to which a patient participates in treatment after agreeing to that regimen
2012	Steiner [46]	Adherence	Interacting behaviors influenced by individual, social, and environmental forces
2012	Vrijens et al. [3]	Medication adherence	Process by which patients take their medications as prescribed

a term that accurately describes the process and personal components leading to patient's performance and (2) definitions have evolved from the reductionist view that "it all comes down" to the authority of physicians, to view adherence as a set of interacting behaviors influenced by social determinants and the ecology of health care [46]. In his definition of compliance, Wright asked "With what?" and criticized the all-inclusive approach to adhere to "everything that is ordered [41]."

Measuring Adherence

New methods to measure compliance were introduced in the 1980s, including pill bottles with microprocessors to record every bottle opening as a presumptive dose confirming that drug compliance is lower in patients receiving higher doses, and pill counts overestimated the frequency of missed doses and serum concentrations of drugs [47]. Compliance is associated with patients' satisfaction, and noncompliance cannot simply be attributed to lack of understanding or memory. Patients actively participate in the monitoring of their health problems the effects of treatment, its adverse effects, and their impact on their normal lives; they are not passively obedient or willfully disobedient in the face of medical expertise. For those reasons, collaboration in doctor–patient relationships is more constructive [48].

Early Interventions to Improve Adherence

Included: (1) letters, telephone**,** or physical reminders to reduce frequency of broken appointments [49–56]; (2) educating medical students about the importance of compliance by experiencing it themselves [52]; and (3) indirect (self-reports, interviews, pill counting, and computerized monitors) and direct methods (biologic markers, tracer compounds, drug concentrations in the patients' biologic fluids) [50]. Strategies to improve adherence involved identifying risk factors of low adherence, simplified and individualized treatment plans, patient education, and aids to improvement, such as labeling and packaging of containers and monitoring by health professionals, patients, and their families [56]. Over the years, the ability of patients to self-monitor biologic parameters including capillary blood glucose [57], blood pressure [58], body mass index [59], or adjusting doses of anticoagulants [60] has been confirmed, and the stages of parallel cooperative monitoring in chronic disease were described and documented [61]. Patients are the leaders of the success of therapy; adherence depends on their decisions.

Interventions to Improve Adherence: The Evidence

In the last two decades, robust methods were introduced to assess interventions to improve adherence to medications including meta-analysis and systematic reviews [62–64] and a series of Cochrane reviews by R Brian Haynes and his colleagues, a pioneer in this field [65–68]. Table 27.2 summarizes the design and results of these reviews:

In conclusion, the analysis of interventions to improve adherence to medications are inconclusive. Nieuwalt and colleagues claimed that "current methods of improving medication adherence for chronic health problems are mostly complex and not very effective…the full benefits of treatment cannot be realized [68]."

Table 27.2 Meta-analysis and reviews of interventions to improve patients' adherence

Date	Author(s) and reference	Methods	Results
1996	Haynes et al. [56]	Systematic review 1553 citations and abstracts screened, 252 reviewed, 13 randomized controlled trials met all the criteria. Diseases analyzed included asthma, hypertension streptococcal throat infection, acute infections, epilepsy, schizophrenia	Disparity in clinical problems, interventions, measures, and reporting of adherence Seven showed improvements in adherence, and six led to improvements in outcomes. Short-term effectiveness using counseling and written information Long-term effectiveness included combinations of quality of care, information, counseling, reminders, self-monitoring, reinforcement, family support, and supervision. Substantial improvements in adherence were not documented.

Table 27.2 (continued)

Date	Author(s) and reference	Methods	Results
1998	Roter et al. [52]	Meta-analysis 153 studies: 116 randomized controlled trials, 37 nonrandom comparisons Interventions or health problems analyzed: Prevention, immunization, or periodic screening Patients discharged from the hospital Hypertension Mental health Diabetes Cancer	Small to large effect sizes for all compliance measures No single strategy or intervention has clear advantages with another. Comprehensive interventions combining cognitive, behavioral, and affective components are more effective than single, isolated interventions.
1998	Haynes et al. [56]	Systematic review 3133 citations and abstracts screened, 345 full text reviewed, 14 randomized controlled trials met all criteria 16 interventions	Eight studies showed improvements in adherence, and six led to improvements in outcomes. Most of the studies were small, introducing the possibility of false-negative error. Some interventions are highly complex and unlikely that their effects were mediated by adherence to medication Unclear potential to generalize, replicate, and disseminate the interventions Difficulties to be carried out in nonresearch settings Most studies did not assess the separate effects of complex interventions involved in chronic disease management. None of the studies examined major clinical endpoints, short-term follow-up: less than 6 to 18 months To achieve full benefits of medical therapies, further innovations are required, including involving investigators from different clinical disciplines.
2002	Mc Donald et al. [57]	Systematic review 6568 citations and abstracts screened, including 101 review articles, 549 full text reviewed, 33 randomized controlled trials met all criteria 39 interventions Disorders studied: Hypertension Schizophrenia, acute psychosis Asthma Chronic obstructive pulmonary disease Depression Human deficiency virus Diabetes Rheumatoid arthritis Epilepsy Hyperlipidemia Acute infections	Number and type of interventions: one to six, including behavioral, cognitive, or social Interventions for short-term treatments: Counseling about the importance of adherence reinforced by written instructions Interventions for chronic treatments: Changes in dosing schedules Remaining interventions are complex and multifaceted, including care at worksites, pill containers, counseling, reminders, self-monitoring, support groups, feedback, and reinforcement. Higher rates of adherence and improvements in blood pressure and glycemic control achieved with innovative interventions, including telephone-linked computer systems for monitoring and counseling patients with hypertension and automated assessment and self-care education calls with nurse follow up for patients with diabetes
2007	Van Dulmen et al. [53]	Review of 38 systematic reviews of the effectiveness of adherence interventions published between 1990–2005	Effective interventions were found in four theoretical approaches: technical, behavioral, educational, and multifaced or complex Technical solutions simplifying therapeutic regimes increase adherence rates; in some cases, they improve clinical outcomes and reduce costs Effective interventions originate from behavioral theories Theoretical models to explain nonadherence are not effective to improve adherence. There is still a scarcity of comparative studies about the effectiveness of theoretical models or their components, which needs to be assessed

(continued)

Table 27.2 (continued)

Date	Author(s) and reference	Methods	Results
2012	Viswanathan et al. [54]	Systematic review of publications assessing the comparative effectiveness of patient, provider, systems and policy interventions that improve adherence to medications From 4124 abstracts, 62 trials about patient–provider interactions or system performance, including 19 interventions and 4 observational studies were analyzed Clinical conditions amenable to improvement: Hypertension Heart failure Depression Asthma	Factors that increase medication adherence: Lower out of pocket expenses Case management Patient education with behavioral support Limited evidence about applicability of interventions or long-term effectiveness
2014	Nieuwlaat et al. [58]	Updated search of the Cochrane library including 109 new randomized clinical trials published since the last update Studies heterogeneous for patients, medical problems, treatment regimens, adherence interventions and clinical outcomes High risk of bias	Findings in comparison with the last update: 1. Lack of convincing evidence among studies with lowest risk of bias. 2. Large heterogeneity, abandon the attempt to classify studies according to intervention. 3. Availability of the database for collaboration on subanalysis. 4. Inconsistent effects from study to study, only a minority of lowest risk of bias RCTs improved adherence and clinical outcomes.

The Role of System Deficiencies on Adherence

The decrease in the mortality by high blood pressure was associated with the appearance of new antihypertensive drugs, but low rates of persistence and huge rates of dropouts resulting in hypertensive crisis and visits to emergency rooms continued to be reported [69, 70]. In 1973, Finnerty and colleagues published a groundbreaking analysis of causes of discontinuation of antihypertensive treatment at an outpatient clinic in Washington in which they identified three leading factors: (1) long waiting times (2.5 hours), (2) deficiencies in doctor–patient relationships (patients were seen by a different physician on each visit), and (3) brief duration of the visit (7.5 minutes) and long waiting times at the pharmacy (1.8 hours) [71]. In response to these deficiencies, 25% of patients believed they were able to treat themselves, 61% agreed to be treated by medical students, and 54.4% agreed to be treated by nurses [71]. Years later, Finnerty reflected that patients dropped out of treatment not because they were uneducated, not because they did not care about their health, and not because they could not afford paying for medications [72]. They abandoned the clinic because "they were treated like cattle, herded from one room to another, left waiting for hours, to be examined by different doctors on each visit [72]." Complaints centered on the amount of time they spent at the clinic and the lack of acceptable, effective relationships with physicians [72].

Hypertension became the prototype disease to describe adherence and its causes. Rudd and Marton described three characteristics associated with failure to achieve blood pressure control: (1) behavioral factors; (2) biologic factors, individual, and unique manifestations of the disease; (3) pharmacologic factors including side effects and combinations of the three [73]. Despite publication of clinical guidelines for hypertension since the1970s, a huge gap still exists between the evidence appearing in controlled clinical trials and what clinicians do in practice and between what clinicians recommend to patients and what patients actually do at home [74]. This gap and its opposite components, clinical inertia (lack of effective physician response) and low patient adherence, are crucial obstacles to providing and receiving adequate quality of care [75]. Compliance of physicians with hypertension guidelines is very low and even worse in patients with diabetes, with the associated increase in cardiovascular risk [76]. Even among patients enrolled in phase IV controlled clinical trials of antihypertensive medications, all patients omit 10% of the doses, including 42% omissions of a single-day dose, 15% on one or two consecutive days, and 47% on multiple days; 95% of the patients miss one dose each month, 48% omit taking medications for 78 hours or more at least once a year, and 13% every 6 months [77].

Measuring Adherence in Hypertension and Beyond

Current methods to measure adherence in hypertension include the Morisky Medication Adherence Scale (MMAS), an eight-item structured, self-reported measure initially

applied in low income, minority patients [78]. Sensitivity and specificity of the MMAS to identify patients with poor blood pressure control is 93% and 53%, respectively; an adherence score in which 8 points were defined as highly adherent, 6–7 points as medium adherent, and less than 6 as low adherent patients is significantly associated with blood pressure control [78]. The MMAS is patient centered, addresses causes leading to voluntary and involuntary suspension of treatment, has been internationally validated [79, 80], and has been applied in patients with diabetes [81].

Adherence and the Complexities of Diabetes Self-Management

Decades ago and still in many places, diabetes was managed from a paternalistic approach: in postwar Germany, patients were admitted to hospitals to stabilize glucose, without receiving training or resources for self-care, and were not allowed to change insulin dosages [82]. Mülhauser and Berger claimed that patient education "had degenerated to obedience training" to follow diets based on fixed amounts of carbohydrates, proteins, and fats, prohibiting sugar intake, which had to be consumed in six to seven meals at fixed times and to obey "doctors' orders" [82]. This approach was ineffective to achieve glycemic control, and acute and chronic complications were frequent. The emotional consequences of diabetes evolved in the construction of a "diabetic personality," in which the daily challenges to confront the disease, its treatment, and consequences were used to explain and attribute poor treatment outcomes on patients in disdain of the enormous scope of expression of individual personalities in adjusting to the daily demands of a healthy lifestyle. This one-dimensional view implied adoption of an inflexible model of behavioral adjustment, rejected by many people [83]. In an early study about adherence in 60 adults with diabetes, Watkins and colleagues reported that 75% did not adhere to diet, 66% were making errors in glucose urine testing, more than 50% made errors in insulin dosage, 50% were giving themselves good foot care, only one patient was deemed completely adherent in the five areas of management, and there was a negative association between knowledge and effectiveness of self-care [84]. In other words, patients in poorer control knew more about diabetes than those under control [84]. In sharp contrast, a diabetes education program that addressed roles of physicians, health providers, patients, and the influence of patients and providers attitudes, behaviors, and skills showed improvements in adherence [85]. This program included (1) a team with a nonthreatening, nonauthoritarian approach; (2) a group process for support, sharing of experiences, and practice according to individual needs; (3) learning by experience rather than conceptual learning to small groups of patients; (4) regular assessment and raising awareness; and (5) innovative techniques inducing changes in health behavior [85].

The multiple self-care activities that patients with diabetes have to carry out on a daily basis to adhere to treatment confirm the need to distinguish the differential difficulties of adhering to medications and to lifestyle changes, but interventions to improve adherence have been inadequate: in 1986, Anderson recognized that diabetes educators lack the time and expertise to become familiar with theories of human behavior and that diabetes education has become an extension of transference of information found in most schools, based on the idea that lack of knowledge and skills accounts for most of poor self-care behaviors [86]. He also claimed that patients' behavior is strongly influenced by their personal view of diabetes and stressed the need that diabetes educators become skilled designers of patient education programs that facilitate changes according to the personal meaning of diabetes [86]. This pioneering concept was associated with the personal model of disease described afterwards by Hampson and colleagues [87].

Nonadherence in Diabetes

The complexities of diabetes management are illustrated by the large variation of adherence to medications, ranging from 36% to 93% in early studies [88–91], while a meta-analysis by Lemstra and colleagues showed that primary nonadherence to antidiabetic medications was 13.2% (95% CI 9.6–16.8) [92]. Adherence to lifestyle changes is even lower; influential factors include (1) comorbidities, (2) cost of therapy or lack of health insurance, (3) adverse family dynamics and codependency, (3) old age, (4) frequency of doses and number of medications, and (5) poor provider–patient relationships and failure in fulfilling patients' health beliefs [93]. Even among patients willing to adhere, additional barriers involve (1) cost of medications, (2) remembering doses, (3) reading prescription labels, and (4) obtaining refills [94]. Additional barriers demonstrate that adherence to one aspect of the regimen is not related to others, and psychosocial variables and situational factors are also important [95, 96]. Nonadherence is not exclusive to diabetes; it occurs in all chronic diseases [97], but it may be even worse in patients with diabetes, taking into account that typical diabetes regimes are complex, life-long, and require introducing multiple behavior changes [97]. The roles and challenges that people with diabetes have to confront were summarized by Bush [97]:

"Of all chronic diseases, diabetes is foremost in putting the responsibility for ongoing health on patients. Proper diabetes treatment requires not simply to take medications and visit the doctor, but to make true lifestyle changes… major and substantial change in behavior is easy to discuss but hard to achieve, and patients may view the treatment of diabetes

worse than the disease itself. The inability of patients to do exactly what we want is so rampant that we have made it a diagnosis: noncompliance [98]."

Methods for Measuring Adherence in Diabetes

These include indirect metrics for clinical settings, indirect metrics for research, and administration and direct metrics, clinical or from laboratory [99–103]. Adherence measures like the Morisky Medication Scale, previously mentioned in this chapter, have also been incorporated [100–103]. Table 27.3 depicts the diverse methods for measuring adherence:

In conclusion according to Anghel and colleagues, "for a method to be ideal in adherence measurement, it should be easy to apply in any setting, accurate and not expensive, and able to provide additional information regarding potential barriers, beliefs, or concerns from patients [101]."

Adherence to Antidiabetics

Table 27.4 shows examples of adherence in people with diabetes [104–114] and confirm that adherence rates are lower than expected in clinical guidelines, even for innovative medications. Median follow-up of studies with GLP-1 agonists range from 2 to 4 years, with persistence rates below 50% at 1 year [115, 116], while adherence to SGLT2 inhibitors is 59.5%, and persistence at 6 months and 1 year is 80.1% and 45.9%, respectively [117]. Taking into account the low rates of adherence and persistence in these studies "from the real world," it is intriguing to consider if these medications will achieve the effectiveness documented in clinical trials of more than 1-year duration. Giving the short duration of persistence, these innovative medications can only demonstrate, as stated by the experts, "non-inferiority as compared with placebo" … without evidence of clinical benefit beyond intermediate outcomes "in the real world [118]."

Table 27.3 Methods used to measure adherence to medications

	Source or definition	Advantages	Disadvantages
Questionnaires	Patient statements about use of medications	Simple	Inaccurate
Self-report	Patient statement of use of medication	Simple	Overestimate adherence No evidence about use of medication
Pill counting	Patient supply of remaining doses	Simple	No actual proof evidence of drug ingestion, daily adherence, or patterns of adherence
Electronic databases	Transmitted report from pharmacy or provider	Inexpensive	No information about individual adherence rates
Electronic monitoring devices	Devices incorporated in drug containers	Precise and detailed information about number of doses taken	False results from incorrect opening of the container
Medication possession ratio (MPR)	Total days supplied/number of days between the first and last refill	Inexpensive	Evidence of drug dispensation, not of actual ingestion
Adjusted medication possession ratio (AMPR)	Total days supply of all prescriptions in defined period/number of days in the defined period	Inexpensive	Evidence of drug dispensation, not of actual ingestion
Proportion of days covered (PDC)	Total days supplied/number of days in refill interval	Inexpensive	Evidence of drug dispensation, not of actual ingestion
Persistence	Period of time without discontinuation	Simple	Evidence of drug dispensation, not of actual ingestion
Daily average consumption	Total number of units dispensed/number of days between index date and date of last refill	Simple	Evidence of drug dispensation, not of actual ingestion
Direct observation	Reception and taking medication at health care facility		Unfeasible for outpatients, impractical
Drug or metabolite levels	Measurement in blood or urine sample	Accurate	Expensive Individual pharmacokinetics Drug interactions
Biologic effect	Measurement of clinical outcomes: blood glucose, blood pressure, lipoprotein profile	Simple	Unable to distinguish from other components of treatment

*Adapted from [99–102]

Table 27.4 Studies about adherence in diabetes management

Year	Author(s)	Patients and intervention	Results and conclusions
2009	Yeaw et al. [99]	Retrospective analysis of pharmacy claims in a database of more than 64 million members Proportion of days covered and persistence among new users of six commonly used chronic medication categories	Six-month persistence for oral antidiabetics (OADs): 66% Odds of discontinuation of OADs significantly lower than for other therapeutic classes
2009	Van Bruggen et al. [100]	Baseline and follow-up data of a randomized controlled trial comparing usual care with care according to a national guideline 30 general practices, 1283 patients Number of prescribed drugs and adherence indices (AI) for oral glucose, antihypertensives and lipid lowering drugs	Higher drug prescriptions in the intervention group An inverse relationship between the number of drugs prescribed during the last 6 months and patients' adherence to blood pressure medications
2010	Fischer et al. [101]	Compilation of e-prescriptions written in 1 year to identify filled prescriptions to evaluate primary non-adherence and identify predictors of nonadherence	78% of prescriptions were filled Higher adherence rates for prescriptions written by primary care physicians Nonadherence for newly prescribed anti-diabetics: 31.4%
2013	Koro et al. [102]	Retrospective analysis of patients with Type 2 diabetes from a national database	Persistence at 6 months: GLP-1 agonists: 31% and DPP-4 inhibitors: 39% Adherence at 1 year: GLP-1 agonists: 11% DPP-4 inhibitors: 18% Other medications: 16%
2016	Alfian et al. [103]	Cross sectional survey in 91 patients with type 2 diabetes using the eight-item Morisky Medication Adherence Scale (MMAS)	Adherence rates: Low: 49.4% Medium: 29.7% High: 20.9% Higher adherence contributes to improved quality of life
2017	Al-Keilani et al. [104]	Cross sectional survey to investigate self-monitoring of blood glucose adherence and predictive factors in 1079 patients with diabetes	Adherence rate: 59% Predictors: Insulin use versus oral antidiabetics Previous diabetes education Knowledge about the use of glucose monitors
2017	He et al. [105]	Retrospective analysis of database insurance claims to assess adherence (≥80.0% possession rate) and persistence (no gaps in insulin therapy during ≥90 days) to insulin therapy and associated factors 24,192 patients with type 2 diabetes	Adherence rate: 30.9% Persistence rate: 53.0% Mean time to nonpersistence: 230.3 days Patients initiated with analogs were more likely to be adherent compared with patients initiated with human insulin. Lower adherence in patients initiated with basal insulin compared with patients initiated with premixed insulin Patients with hypertension, dyslipidemia, treated with prandial insulin, or with severe hypoglycemia were more likely to be nonadherent/nonpersistent
	Lin et al. [106]	Retrospective study to assess treatment persistence and associated outcomes in 7320 patients with type 2 diabetes treated with a GLP-1 agonist in combination with basal insulin	Treatment persistence: 16.9% Median time to discontinuation: 133 days Persistent patients had greater A1c reductions, were more likely to achieve A1c <7.0%, were less likely to experience hypoglycemia, had fewer hospitalizations and were less likely to experience hypoglycemia Total medical charges were significantly lower for persistent patients

(continued)

Table 27.4 (continued)

Year	Author(s)	Patients and intervention	Results and conclusions
	Flory et al. [107]	Retrospective study of a cohort of 11,067 patients from a database including information on more than 120 million commercially insured and Medicare Advantage enrollees Unit to measure adherence: "daily medication possession probability" (MPP): days of supplied prescription/number of patients in the cohort	Clear separation of adherence between drug classes after 90 days Daily MPPs: Sulfonylureas: 0.49 Metformin: 0.46 Basal insulin: 0.39 Glitazones: 0.36 GLP-1 agonists: 0.30 DPP-4 inhibitors: 0.21 Particular attention needs to be paid to adherence issues with newer drug classes, that is, GLP-1 agonists and DPP-4 inhibitors Substantial differences between rates at which diabetes drugs are prescribed and rates at which patients actually take them
2020	Alsheri KA et al. [108]	Cross sectional analytic study self-completed questionnaire 387 patients with type 2 diabetes	68.5% reported adherence toward their medications Reasons for nonadherence: Forgetting to take medications: 67.21% Use for long periods of time: 50% Polypharmacy: 44.26% Complexity of therapeutic regime: 40.16% Lack of family support: 38.52% Side effects of medication: 35.24% Interference with meal plan: 35.24% Feeling that doses were too high: 30.32% Feeling that treatment was ineffective: 24.59% Insufficient economic resources: 13.11%
2021	Romagnoli A et al. [109]	Retrospective observational study; dispensations delivered at the pharmacy of a general hospital over 9 years Adherence and persistence estimation over 3 years using the pharmacy-refill method 19,600 patients with type 2 diabetes	Absolute adherence at 3 years: 0.68; per therapeutic class: GLP-1 analogues: 0.99 SGLT2i: 0.87% DPP4i: 0.85 Glitazones: 0.84 Sulfonylureas: 0.77 Metformin: 0.64 Alpha-glucosidase inhibitors: 0.62 Meglitinides: 0.49

Behavioral Aspects

Adherence in diabetes became a conceptual and empirical enigma. Studies related to the health belief model, social learning theory, and interpersonal relationships about determinants of adherence behaviors are important in clinical practice [119, 120]. Models explaining individual health-related behaviors include the "Health Belief Model" (HBM) [120, 121]. The basic components of the HBM originated from the "value expectancy" approach of Levin in 1944 [122], to describe behavior or decision-making under uncertainty. Its main elements include (1) the state of readiness to address a particular health problem and the perception of threat represented by illness; (2) the belief in the personal efficacy to reduce the threat, consequences, and perceived barriers involved in action; and (3) "cues to action," external, or internal "triggers" inducing the appropriate health behavior [121, 122].

In the traditional approach to health behavior change, physicians are seen as the experts who know what is best for the patient, based on the assumption that all patients should change their behavior, all have the same willingness to change, and diseases and treatments are their most important priorities [123]. This assumption is not valid: lack of concordance between patients and providers and divergences in the approach to health status have been repeatedly described in people with diabetes. Beyond agreements in perception of severity, large disparities prevail about the effect of adherence on the cost of therapy and its benefits [124]. Patient–provider discrepancies, low levels of agreement between patients and physicians (kappa =0.23) about adherence to diabetes treatment, have been reported worldwide and are influential on glycemic control [124–126].

Psychological Issues and Adherence in Diabetes

The importance of psychological aspects on diabetes was documented since the seventeenth century when Willis and Maudsley noted that prolonged depression or anxiety appeared to cause diabetes [127]. Reports from the nineteenth century provided a conceptual framework to support that emotional disruption antedates metabolic decompensation

[127]. Further studies about psychological aspects of diabetes identified four important topics: (1) association with the onset of the disease; (2) the influence of the environment on its course; (3) the immediate response and long-term personal adjustment; and (4) the reaction of the family to the illness and its impact on the family structure [128–130]. Research has shown a clear relationship between diabetes and mental health, including psychiatric disorders and problems specific to the experience of living with diabetes [130].

Russell Glasgow, a pioneer and leader on the study of behavioral aspects of diabetes and chronic disease management, described the limitations of applying traditional compliance terms in patients with diabetes, ignoring the complexity of self-care [131]. He stated that "in addition to taking medicines, people with diabetes have to carry out multiple activities including lifestyle changes and blood glucose monitoring, frequently not communicated or measured [132]." He claimed that having diabetes, treating diabetes, or developing diabetic complications have their own psychological impact, and quantitative measurements are essential to account for the complex interactions between personal and environmental factors that facilitate or hinder adjustment and coping, including adherence [133]. Glasgow and colleagues published studies about the importance of supportive and nonsupportive factors on adherence and glycemic control, including family influences [134] and psychosocial correlates on self-care behaviors [135–137]. From this perspective, adherence should be considered in the context of other factors, instead of assuming that it is simply the result of one-to-one interactions between patients and physicians. Analysis of psychosocial factors related to self-management resulted in the description of "personal models of disease," including disease-related beliefs, emotions, knowledge, and experiences [137]. Glasgow and associates described the concept of personal models of disease in diabetes and their predictive value to carry out self-care activities related to adherence and glucose control [138]. The consistency of personal models of "perceived treatment efficacy (PTE)" as barriers or facilitators to self-management has been confirmed and patient "noncompliance" may be the result of impaired PTE [139]. If patients do not believe that medical recommendations contribute to a positive impact on their health, it is understandable that they might lose motivation [139].

Behavioral Strategies to Improve Adherence

Motivational Interviewing

Having good intensions to engage in healthy behaviors to change one's life in a positive direction may not always translate into actions or behavior that is maintained [140]. Motivational interviewing arose from experiences acquired in the management of alcoholism [141], a complex disease with social, personal, and behavioral components in which the authoritative medical approach had been unsuccessful. Motivational interviewing has its roots on Bandura's self-efficacy theory, which he defined as "a judgment of one's ability to organize and execute given types of performances [142]." Bandura explained that people have always striven to control events affecting their lives and that the growth of knowledge over human history enhanced people's ability to predict events and try to control them [142]. Beliefs in supernatural levels of control (i.e., physician's authority over patient's everyday behaviors) are surpassed by conceptions that acknowledge the people's power to shape their own destiny [142]. Changing threatening health behaviors and following medical advice are important components of almost every medical interaction, but they can be difficult to accomplish; practitioners commonly end up making cursory attempts to satisfy their perception of the problem or avoiding the topic [143]. Telling or threatening people that they will "pay the consequences" if they do not change their lifestyle or take medications is rarely enough to change behavior [143]. People change and follow doctor's orders under the guidance or influence of individual, unique perceptions. Motivational interviewing promotes behavior change in a wide range of health care settings requiring lifestyle changes, including the "big four" lifestyle habits (smoking, excessive drinking, lack of exercise, and unhealthy diet [144]), adherence to treatment for obesity, diabetes, and infection with HIV [145]. Motivational interviewing is based on the recognition that advising or ordering patients to change is often unrewarding and ineffective, and a key component is to acknowledge that patients have every right to make no change [140, 146]. Instead of directive approaches, motivational interviewing requires a guiding style to engage with patients, identify strengths and limitations, encourage motivation for change, and promote the autonomy of decision making [145]. Application of motivational interviewing in diabetes management in pediatric and adult populations is highly appealing [140, 147]. It has a positive influence on diabetes outcomes, but the number of published studies is still scarce and heterogeneous, patient participation is unpredictable, and long-term assessment is scarce [147–149].

Diabetes Empowerment

There are two approaches to diabetes patient education: one is obedience based and another is based on empowerment [150]. From that perspective, adherence and compliance are dysfunctional concepts [151]. Patient empowerment (PE) stems from a broader philosophical concept of empowerment introduced by the Brazilian pedagogue Freire in the 1970s and was linked in health care in the early 1990s in the United States [152]. Born as a reaction to societal oppression and inequal-

ity, PE was adopted in other disciplines and transformed as a multidisciplinary concept. Empowerment implies that human beings have the potential to make choices and gain control of their life [152]. The unique role and responsibilities of patients in the daily treatment of diabetes can be recognized from the premise that people have the capacity to make choices and are responsible for their consequences [152–154]. The goals of diabetes empowerment are enabling patients to make informed decisions about their personal diabetes care and to be fully responsible members of the health care team [154]. Empowerment offers a practical conceptual framework for diabetes education and provides patients with the knowledge, skills, and responsibility to change, promote health, and maximize the use of available resources [155]. Empowerment is defined as "the discovery and development of one's inborn capacity to be responsible for one's own life [156]." It was designed to help patients develop knowledge, skills, attitudes, and self-awareness to assume the responsibility for their health-related decisions [154]. People are empowered when they have (1) enough knowledge to make rational decisions, (2) enough control, (3) enough resources to implement their decisions, and (4) enough experience to evaluate the effectiveness of their actions [156]. By comparison with traditional medical approaches, empowerment is not something one does to patients: empowerment begins when healthcare professionals acknowledge that patients are the ones who really have the control of their daily diabetes care [157]. Empowerment occurs when the health professional's goal is to increase the capacity of patients to think critically and make autonomous, informed decisions [154]. The success of PE seems to be due to the political views of society and loss of confidence in health-care professionals, especially physicians, who should "come down off their pedestal [152]." It has been shown that diabetes empowerment improves diabetes knowledge, medication adherence, and self-care behaviors [158], but the number of published studies is small; large-scale implementation at a national or system level has not been accomplished.

Addressing Adherence

Adherence is not dependent of characteristics traditionally perceived by physicians like sex, race, or age. Besides information and communication problems, prejudice from clinicians reduces their capacity to understand patients' needs, their resources, and willingness to change [159]. Using "adherence aids," including pill boxes, putting pills in special places, and associating pill taking with daily events like meals has shown limited effectiveness [160]. Failure of patients to attend medical visits, monitoring glucose, or taking medications impairs diabetes control, but failure of physicians to intensify therapy in patients not achieving the goals (clinical inertia) is probably more important than patients' adherence [161–163]. Adherence depends on a variety of interacting factors on increasing impact like comorbidity and polypharmacy [105]. Several studies have shown positive and significant relationships between social support and adherence to diabetes therapy, but the exact mechanism by which social support affects patients' adherence is not completely understood [164]. Emphatic engagement is also important and may even reduce the frequency of acute complications [165]. Competence and skills to overcome clinical inertia and assist patients to increase adherence, instead of just reiterating what they should be doing and putting the blame on them if they fail, is also a key component of success in diabetes care [166].

In recognition of its importance, The World Health Organization (WHO) published a report in 2003 enlisting five interacting dimensions of adherence: (1) social and economic, (2) related to health systems, (3) condition-related, (4) therapy-related, and (5) patient-related [44]. System-related factors have negative effects on adherence and outcomes, including deficiencies of health services, poor medication distribution systems, limited knowledge and training of health professionals about adherence, and effective interventions for improvement [44].Take-home messages from the WHO Report highlight the importance of adherence and the influence of patients on outcomes [44]:

1. Poor adherence to treatment is a worldwide problem of huge magnitude.
2. Poor adherence will grow as the burden of chronic disease that continues to increase.
3. The consequences of poor adherence to long-term therapies include poor clinical outcomes and increased healthcare costs.
4. Improving adherence also improves patients' safety.
5. Adherence is an important modifier of the effectiveness of health systems.
6. Increasing the effectiveness of adherence interventions will have a greater impact on population health than advances in medical therapy.
7. Patients need to be supported, not blamed.
8. Adherence is simultaneously influenced by several factors.
9. Health professionals need to be trained about adherence.

Modified from the World Health Organization report [44].

Conclusions

In a lecture "upon medical ethics," Ingelfinger stated that "if you agree that the physician's primary function is to make the patient feel better, a certain amount of authoritarianism, pater-

nalism, and domination are the essence of physician's effectiveness [167]." Millions of doctors worldwide still believe that persuasion and mind bending are necessary to be "effective physicians [11]." Seven decades of efforts led to understand adherence from the patients' perspective, starting with the need to change semantics, to advance from myths like "uncooperativeness" or "noncompliance" to adherence, still an inaccurate term [168]. A new language of medication taking has been waiting for decades and will be more important as the authority of patients in decision-making and in the successful management of chronic disease is recognized [169–175]. Steiner and Earnest suggested that to improve the language of medication taking, the terminology has to change because patients have the most important opinion about the best strategy to increase medication taking. In this novel approach, physicians have to ask about medication taking, they to be prepared and willing to reply to questions, outcomes have to be emphasized, and the importance of medication taking has to be explained to achieve the expected results of therapy [169]. Nonadherence is still barely on the radar of most practicing physicians who remain unaware about it [170]. Improving adherence requires an active process of behavioral change involving education, motivation, tools, support, monitoring, and evaluation [170]. Approaches to improving adherence and persistence include reducing treatment complexity, using medications with improved safety profiles, improving communication and patient support, and awareness about its existence and influence on outcomes [171].

Multiple Choice Questions

1. What is the best term to describe the patients' expected behavior to medical recommendations:
   (a) Obedience
   (b) Compliance
   (c) Adherence
   (d) **None of the above**
   (e) All of the above
2. Traditional methods to assess adherence include:
   (a) Direct interrogation of patients and their families
   (b) Residual medication counting
   (c) Measurement of drug metabolites
   (d) **All of the above**
   (e) None of the above
3. More than 30 years ago, it was confirmed that compliance is not related to income, social class, occupation, or education:
   (a) **True**
   (b) False
4. The word "compliance" implies:
   (a) That patients are obeying as expected
   (b) The effectiveness of treatment
   (c) **That patients are willfully disobedient in the face of medical expertise**
   (d) That results of controlled clinical trials can be replicated "in the real world"
   (e) All of the above
5. It has been shown that patients are able:
   (a) To self-monitor blood glucose levels and adjust insulin doses
   (b) To self-monitor blood pressure levels and adjust antihypertensive doses
   (c) To self-monitor body mass index to achieve sustained body weight loss
   (d) **All of the above**
   (e) None of the above
6. Discontinuation of chronic disease treatment is highly associated with:
   (a) Patients' ignorance
   (b) **Long waiting times to receive the medical visit**
   (c) **Deficiencies in doctor–patient relationships**
   (d) The economic status of patients
   (e) Insufficient intelligence to understand physicians' orders
7. The "diabetic personality" refers:
   (a) To the consequences of diabetes on mental health
   (b) **To the attribution of poor treatment outcomes on the patients' fault**
   (c) To the adaptation process to diabetes and its demands
   (d) To the existence of a single, well-defined personality of all people with diabetes
8. Total adherence to all the components of diabetes management is estimated at:
   (a) 100 percent
   (b) 80 percent
   (c) 50 percent
   (d) 25 percent
   (e) **1 percent**
9. Nonadherence to diabetes diet has been reported at:
   (a) 100 percent
   (b) **75 percent**
   (c) 66 percent
   (d) 50 percent
   (e) 25 percent
10. Errors in insulin dosage by patients have been reported at:
    (a) 100 percent
    (b) 75 percent
    (c) 66 percent
    (d) **50 percent**
    (e) 25 percent

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Part V

Resources of Support for Persons with Diabetes

Challenges and Opportunities in Diabetes Education

28

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Definition of Diabetes Self-Management Education and Support

The National Standards for Diabetes Self-Management Education were first developed in the United States in 1995. These standards serve as guidance for those providing diabetes education and set the standard for best practice in developing, implementing, and evaluating a diabetes self-management education program [1]. In 2011, a task force representing the Association of Diabetes Care and Education Specialists and the American Diabetes Association changed the name to National Standards for Diabetes Self-Management Education and Support [2]. In the most recent version, the standards include the following definition:

> Diabetes Self-Management Education and Support (DSMES): an ongoing process of helping people with diabetes develop problem-solving skills to enhance and improve the decision-making necessary to self-manage diabetes on a continual basis. DSMES services support measurable, meaningful, and sustainable behavior change. DSMES interventions include activities that support a person in implementing and sustaining the behaviors needed to manage his or her condition on an ongoing basis [3].

Diabetes Canada states the following:

> Self-management education (SME) is a process to facilitate individuals in decision-making, resulting in improvements in variables, such as knowledge, attitudes, and self-efficacy, as well as improvements in healthy behaviors and clinical outcomes. SME is defined as a systematic intervention that involves active participation by the individual in self-monitoring of health parameters and/or decision-making with the application of knowledge and skills. It also recognizes that patient–provider collaboration, approaches, and the development of problem-solving skills are crucial for sustained self-care. Self-management support (SMS) includes activities that support the implementation and maintenance of behaviors for ongoing diabetes self-management, including education, behavior modification, and psychosocial and/or clinical support. The goal of SME and SMS is to foster opportunities for people with diabetes to become informed and motivated to continually engage in effective diabetes self-management practices and behaviors [4].

Other countries have comparable definitions that can often be found on their websites.

Evidence Supporting the Effectiveness of Diabetes Education

Structured diabetes self-management education and support programs lead to reduced A1C [5–10], reduced all-cause mortality in people with type 2 diabetes [11], improved self-care activity [10], and sometimes result in weight loss [7]. An integrative review that studied pediatric diabetes self-management education and support programs showed that mixed programs containing both self-care aspects and psychosocial aspects, and delivered online, were most likely to influence psychosocial competencies in children and adolescents [12]. Diabetes self-management education and support has also demonstrated cost-effectiveness [11, 13] and improved quality of life in people with diabetes [6, 14, 15].

Recommendations for Diabetes Education

The American Diabetes Association states that ongoing diabetes self-management education and support are critical to preventing acute complications and reducing the risk of long-term complications. (ADA 2022) They recommend that all people with diabetes should participate in diabetes self-management education and receive the support needed to facilitate the knowledge, decision-making, and skills mastery necessary for diabetes self-care. They further state that

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there are four critical times to evaluate the need for diabetes self-management education to promote skills acquisition in support of treatment plan implementation, medical nutrition therapy, and well-being. These four times correlate to times when people with diabetes may need the most assistance to achieve and/or adjust their goals and care plans for effective daily self-management [16].

The International Diabetes Federation also includes "the right to information and education" in their Charter of Rights and Responsibilities for People with Diabetes. In addition, an individualized medical nutrition therapy program, preferably by a registered dietitian, is recommended for all people with diabetes.

Diabetes Australia recommends structured diabetes education to consumers as soon as possible after diagnosis, ongoing, and on request. They also recommend diabetes education that is person-centered, promotes active learning, and has the flexibility to meet individual needs, choices, and learning styles [17]. Diabetes UK published a report titled, Diabetes Education: The Big Missed Opportunity in Diabetes Care, highlighting their view that diabetes education is an essential part of managing diabetes and avoiding long-term complications [18]. The National Institute for Health and Care Excellence also recommends structured diabetes education programs and points to Diabetes UK guidelines on their website [19].

The DAWN2 Study sought cross-national comparisons across 17 countries of perceptions on health care provision for benchmarking and sharing of clinical practices to improve diabetes care. Results of quantitative surveys of almost 9000 people with diabetes, family members, and health-care professionals drew attention to the large number of people who feel the burden of the disease and made the case for improved psychosocial care and diabetes self-management education. Specifically, about half of the people surveyed with diabetes reported diabetes has a negative impact on their physical health and emotional well-being. Just less than half (45%) reported experiencing diabetes-related distress [20]. The Association of Diabetes Care and Education Specialists promotes using a person-centered approach when working with people living with diabetes. This includes asking people how they are doing, finding out what is working and not working, and taking into consideration their personal values, needs, and preferences, and using shared decision-making when setting goals [21].

While standards from major diabetes organizations are recognized worldwide, how do these recommendations get interpreted and operationalized? Access to diabetes education and diabetes educators varies greatly around the globe. The following section includes highlights from some of the major position papers and practice guidelines, which can be tailored for diverse practice settings.

Standards for Diabetes Education

In 2019, the American Association of Diabetes Educators (AADE) announced a name change for the diabetes education specialty. Diabetes education was changed to diabetes care and education to better reflect the broader scope and focus of the specialty [22]. In the United States, diabetes educators are now diabetes care and education specialists, and in 2020, the AADE became the Association of Diabetes Care and Education Specialists. In addition, the credentialing board for the specialty is now the Certification Board for Diabetes Care and Education and accordingly, the former Certified Diabetes Educator credential is now the Certified Diabetes Care and Education Specialist (CDCES). "Diabetes educator" and "Certified Diabetes Educator" are used in this chapter, where applicable, because these terms continue to be recognized internationally.

The process and quality of diabetes education is guided by standards and guidelines. In the United States, the National Standards for Diabetes Self-Management Education and Support (National Standards, 2022) define quality diabetes self-management education and support and assist those who educate to implement evidence-based programs and services. In the United States, diabetes education services must meet the National Standards in order to bill for education services. Additionally, the standards provide expert recommendations to anyone setting up and/or improving educational services. The National Standards are reviewed and updated every 5 years by a multidisciplinary group representing the American Diabetes Association and the Association of Diabetes Care and Education Specialists. The standards define such things as who can provide diabetes education, content areas to be assessed and taught as needed, importance of providing ongoing support, and quality. The national standards provide a helpful guideline for setting up diabetes education services.

While the National Standards highlight the benefit of a team approach to diabetes education, they also acknowledge that a team is not always possible or available. To meet quality standards, it is recommended that diabetes education be delivered by a nurse, dietitian, or pharmacist with relevant background and experience. For example, in the United States, 15 hours of continuing education per year in diabetes-related topics is considered a minimum acceptable level of instruction. Qualification as a certified diabetes care and education specialist may be obtained by a wide variety of clinicians within the United States, including nurses, dietitians, pharmacists, physicians, clinical social workers, and master's level exercise physiologists [23].

Eight core content areas are defined within the National Standards. An assessment of each individual's needs

determines which elements of the curriculum are required. Content areas include the following:

- Pathophysiology of diabetes
- Healthy coping
- Healthy eating
- Being active
- Medication use (treatment options including diabetes devices)
- Monitoring (including use of diabetes devices)
- Problem solving
- Reducing risks (treating acute and chronic complications such as hypoglycemia and hyperglycemia and chronic complications such as cardiometabolic, vision, hearing, dental, and foot care)

Other recommended content areas include navigating the healthcare system, self-advocacy, and e-health education.

The National Standards highlight the importance of person-centered, interactive, and evidence-based diabetes education. The most successful approach is one in which patients and providers work together to develop an individualized education plan. Evidence-based communication and behavior change strategies are also recommended, including collaborative goal setting, motivational interviewing, and interactive teaching techniques. In addition, the Standards address the need for ongoing support, measuring participant progress, and continuous quality improvement.

Health-care professionals can look for diabetes education standards that may have been written for a country or health system in a specific region, as a variety of them do exist. Notably, the International Diabetes Federation has published a detailed collection of 32 standards that describe not only structure and process standards (recommended elements of a diabetes program similar to those described in the US National Standards document) but also content standards (describing what to assess and teach) and outcomes standards (what to measure) [24].

The roles and expectations for diabetes educators vary greatly around the world. In the United States, many diabetes educators with advanced credentialing work closely with the physician—and other health care providers—as a co-manager of the patient's care. This may involve reviewing blood glucose patterns (from meter or continuous glucose monitoring downloads) and making recommendations to the physician for treatment changes and/or adjusting insulin within established guidelines. Some diabetes educators are expected only to deliver information about diabetes to patients, having little interaction with the physician or even input from the patient. The latter is not an ideal model. Instead, collaboration and communication among all team members is most beneficial for the best outcomes.

The Association of Diabetes Care and Education Specialists has defined competencies for the diabetes educator and for nonclinical providers such as community health workers or promotors (see Table 28.1). For each of these levels, competencies (minimal skills and knowledge) have been recommended in six domains (see Table 28.2):

1. Clinical management practice and integration
2. Communication and advocacy
3. Person-centered care and counseling across the lifespan
4. Research and quality improvement
5. Systems-based practice
6. Professional practice [25]

Self-assessment worksheets, available on the Association of Diabetes Care and Education Specialists website, are useful for evaluating where additional training, and support may be needed to enhance skills in each of the domains [26].

In the past, there was a lack of clarity regarding when to provide and modify DSMES. The DSMES Consensus Report of the American Diabetes Association, the Association of Diabetes Care and Education Specialists, the Academy of Nutrition and Dietetics, the American Academy of Family Physicians, the American Academy of PAs, the American Association of Nurse Practitioners, and the American Pharmacists Association defines four critical times for diabetes self-management education and support services [16].

Table 28.1 Diabetes educator provider levels

Diabetes community care coordinators	Health professionals	Diabetes care and education specialists
Member of the diabetes care team focused on linking individuals to resources, building relationships, and supporting people with, affected by, or at risk for diabetes and cardiometabolic conditions. This includes, but is not limited to, community health workers (CHW), health educators/coaches, medical assistants (MA), certified nursing assistants (CNA), licensed practical nurses (LPN), registered nutrition/dietetic technicians (NDTR), military medics and corpsmen, pharmacy assistants/technicians, physical therapy assistants, nutritionists, dental hygienists, emergency medical technicians (EMT), and other similar roles.	Member of the diabetes care team who interacts with people with diabetes and related conditions, but whose primary focus is not diabetes. This includes, but is not limited to, registered nurses (RN), registered dietitian nutritionists (RDN), pharmacists, and other similar roles.	Experts who, as integral members of the care team, provide collaborative, comprehensive, and person-centered care and education to people with diabetes and related conditions. This includes, but is not limited to, those with the credential CDCES (certified diabetes care and education specialist) or BC-ADM (board certified advanced diabetes management) and similar roles specializing in diabetes.

Table 28.2 Competencies for those working in diabetes care and education

Domain 1: Clinical Management Practice and Integration
The diabetes care and education specialist integrates knowledge and skills into clinical practice applying principles of pathophysiology, epidemiology, clinical management, and self-management of diabetes and cardiometabolic conditions.
Domain 2: Communication and Advocacy
The diabetes care and education specialist advocates for and communicates about improved quality of care and outcomes for those living with, at risk for, and affected by diabetes and cardiometabolic conditions.
Domain 3: Person-Centered Care and Counseling Across the Life Span
The diabetes care and education specialist partners with individuals to deliver care and education conducive to behavior change and improved quality of life for self-management of diabetes and cardiometabolic conditions across the life span.
Domain 4: Research and Quality Improvement
The diabetes care and education specialist contributes to research and quality improvement activities and applies current research and evidence-based care to guide practice.
Domain 5: Systems-Based Practice
The diabetes care and education specialist applies business principles, systems practice, and population health management to support achievement of the Quadruple Aim (reduced costs, better outcomes/population health, improved patient experience, and improved work life for health care providers).[16]
Domain 6: Professional Practice
The diabetes care and education specialist engages in lifelong learning and serves as a role model of professionalism.

Source: Ref. [24]

This report specifically addresses type 2 diabetes, yet it is applicable for all types of diabetes.

Following are the four critical times to provide and modify DSMES:

- At diagnosis—to teach survival skills to address immediate requirements (safe use of medication, hypoglycemia treatment if needed, introduction of eating guidelines; to assess individual preferences and barriers to implement self-management needs)
- Annually and/or when not meeting treatment targets—to assess certain situations such as elevated A1C, unexplained highs or lows, or planning a pregnancy
- When complicating factors influence self-management—such as a diagnosis of retinopathy or cancer, or the occurrence of a stroke or factors, such as a broken arm, that affect movement like the ability to do physical activity, prepare meals, and utilize monitoring devices—that can affect glucose management
- When transitions in life and care occur
- (aging, living situation, schedule changes, or health insurance coverage).

To maximize the team approach to care and education, the Consensus Report includes a list of factors that indicate when a referral is needed (Table 28.3) and a checklist of general responsibilities for providers and their teams and the diabetes care and education specialist at each of the four critical times (Table 28.4). Figure 28.1 is a visual depiction of the four critical times and content focus areas. The figure can be used during self-management education or training of health professionals to highlight the times, content, and benefit of diabetes self-management education and support. A recent paper adopted this figure to be specific to those with type 1 diabetes [27]. Additional resources that support increased participation in diabetes self-management education and support are available at diabeteseducator.org/consensusreport.

Table 28.3 Factors that indicate referral to diabetes education services is needed

At diagnosis
• Newly diagnosed--all newly diagnosed people with type 2 diabetes should receive diabetes education. • Ensure that both nutrition and emotional health are appropriately addressed in education or make separate referral.s
Annually and/or when not meeting treatment targets
• Review of knowledge, skills, psychosocial, and behavioral outcomes or factors that inhibit or facilitate achievement of treatment target and goals • Long-standing diabetes with limited prior education • Treatment ineffective for attaining therapeutic target • Change in medication, activity, or nutritional intake or preferences • Maintenance of clinical and quality of life outcomes • Unexplained hypoglycemia or hyperglycemia • Support to attain or sustain improved behavioral or psychosocial outcomes
When complicating factors develop
Change in: • Health conditions, such as renal disease and stroke, need for steroids, or complicated medication regimen • Health status requiring changes in nutrition, physical activity, and so forth • Planning pregnancy or pregnant • Physical limitations such as cognitive impairment, visual impairment, dexterity issues, and movement restrictions • Emotional factors such as diabetes distress, anxiety, and clinical depression • Basic living needs such as access to shelter, food, health care, medicines, and financial limitations
When transitions in life and care occur
Change in: • Living situation such as inpatient or outpatient or other change in living situation (i.e., living alone, with family, assisted living, etc.) • Clinical care team • Initiation or intensification of insulin, new devices or technology, and other treatment changes • Insurance coverage that results in treatment change (i.e., provider changes, changes in medication coverage) • Age-related changes affecting cognition, vision, hearing, self-management, and so forth

Source: Adapted and reprinted with permission from The American Diabetes Association. Copyright 2020 by the American Diabetes Association [15]

Table 28.4 Checklist for providing and modifying diabetes education at four critical times

Primary care provider/ endocrinologist/clinical care team's role in diabetes education	Diabetes care and education specialist's role in diabetes education
At diagnosis (series of visits)	
• Answer questions and provide emotional support regarding diagnosis • Shared decision-making of treatment and treatment targets • Teach survival skills to address immediate requirements (safe use of medication, hypoglycemia treatment if needed, introduction of eating guidelines) • Identify and discuss resources for education and ongoing support • Make referrals for diabetes education and medical nutrition therapy (MNT)	• Assess cultural influences, social determinants of health, health beliefs, current knowledge, physical limitations, family support, financial and work status, medical history, learning preferences and barriers, literacy, and numeracy to determine which content to provide and how: • Medication – choices, access, action, titration, side effects • Monitoring blood glucose – when to check, interpreting and using glucose pattern management for feedback • Physical activity – safety, short-term vs. long-term goals/recommendations • Preventing, detecting, and treating acute and chronic complications • Nutrition – food plan, planning meals, purchasing food, preparing meals, portioning food • Risk reduction – smoking cessation, foot care, cardiac risk • Developing personal strategies to address psychosocial issues and concerns; adjusting to a life with diabetes • Developing personal strategies to promote health and behavior change • Problem identification and solutions • Identifying and accessing resources
Annually and/or when not meeting treatment targets	
• Refer for new techniques, technology, and updated information • Assess and refer if self-management targets not met to address barriers to self-care	• Review and reinforce treatment goals and self-management needs • Review barriers to treatment effectiveness • Emphasize preventing complications and promoting quality of life • Discuss how to adjust diabetes treatment and self-management to life situations and competing demands • Support efforts to sustain initial behavior changes and cope with the ongoing burden of diabetes

(continued)

Table 28.4 (continued)

Primary care provider/ endocrinologist/clinical care team's role in diabetes education	Diabetes care and education specialist's role in diabetes education
When complicating factors develop	
• Identify presence of factors that inhibit or facilitate achievement of treatment targets and personal goals • Discuss impact of complications and successes with treatment and self- management	• Provide support for the provision of self-management skills in an effort to delay progression of the disease and prevent new complications • Provide/refer for emotional support for diabetes-related distress and depression • Develop and support personal strategies for behavior change and healthy coping • Develop personal strategies to accommodate sensory or physical limitation(s), adapt to new self- management demands, and promote health and behavior change
When transitions in life and care occur	
• Develop diabetes transition plan • Communicate transition plan to new health-care team members • Establish diabetes education regular follow-up care	• Adjust diabetes self-management plan as needed • Provide support for independent self- management skills and self-efficacy • Identify level of significant other involvement and facilitate education and support • Assist with facing challenges affecting usual level of activity, ability to function, health benefits and feelings of well-being • Maximize quality of life and emotional support for the person with diabetes (and family members) • Provide education for others now involved in care • Establish communication and follow-up plans with the provider, family, and others • Develop goals and personal strategies to promote health and behavioral change and improve quality of life

Source: Adapted and reprinted with permission from The American Diabetes Association. Copyright 2020 by the American Diabetes Association [15]

Fig. 28.1 The four critical times to provide and modify diabetes self-management education and support. Source: Adapted and reprinted with permission from The American Diabetes Association. Copyright 2020 by the American Diabetes Association [15]

Challenges in Meeting Diabetes Education Needs: Addressing the Problem

Each individual with diabetes benefits from initial and ongoing diabetes education and support to address the day-to-day behaviors that impact health and quality of life. The 422 million people diagnosed with diabetes worldwide require this intervention so each can effectively manage their diabetes on a daily basis [28]. (ADA, 2022) Diabetes education includes much more than medication teaching; therefore, it is a valuable intervention regardless of when diabetes medications are started. At diagnosis, the provider and diabetes educator has the opportunity to address fears and myths about diabetes, provide emotional support and answer questions, and set the stage for living well with a chronic disease that requires focus, hope, and resources to manage on a daily basis [16]. Also, this is a time that involves collaborative discussion and decision-making related to medications, monitoring, physical activity, complications, nutrition, risk reduction, and developing personal strategies to address psychosocial issues and concerns and to promote health and behavior change [16].

A unique comparison of diabetes education and support to metformin highlights the many medical, nutritional, and behavioral benefits of education and support (See Table 28.5) [29] and points out that if diabetes education were a pill it would be routinely prescribed. Table 28.6 further delineates these benefits and highlights the intrinsic necessity of offering access to education and support at all four critical times [16].

Challenges in meeting an individual's diabetes education and support needs include knowing what education and support is needed, having qualified staff to engage in this clinical care, and ensuring patients continually access this care as their diabetes care needs change.

Table 28.6 Summary of diabetes education benefits to discuss with people with diabetes

Provides critical education and support for implementing treatment plan	Promotes lifestyle behaviors including healthful meal planning and engagement in regular physical activity
Reduces emergency department visits, hospital admissions, and hospital readmissions	Addresses weight maintenance or loss
Reduces hypoglycemia	Enhances self-efficacy and empowerment
Reduces all-cause mortality	Increases healthy coping
Lovers A1C	Decreases diabetes-related distress
	Improves quality of life
No negative side effects	
Medicare and most insurers cover the costs	

Source: Adapted and reprinted with permission from The American Diabetes Association. Copyright 2020 by the American Diabetes Association [15]

Identify Education and Support Needs

There are a number of position statements, consensus papers, standards of care and curricula that detail topics to address in diabetes care. Many of these highlight the need to offer education in a person-centered, collaborative, engaging, and respectful manner. There are basic needs that should be addressed immediately upon diagnosis by the diabetes care team and then other needs that can be addressed soon after either through a diabetes education program or by dedicated education staff within the clinic [16].

The DSMES Consensus Report discussed earlier details on the breadth of education required for daily self-management of diabetes at the four critical times. It includes a valuable checklist for providing and modifying DSMES at four critical times (Table 28.4). The checklist summarizes the when and what of diabetes education. It offers guidance on which members of the health-care team could provide the needed education and is a useful tool for the team to discuss to ensure your patients are receiving the care they need.

Table 28.5 Comparing the benefits of diabetes education versus metformin therapy

	Benefits rating	
Criteria	Diabetes education	Metformin
Efficacy	High	High
Hypoglycemia risk	Low	Low
Weight	Neutral/loss	Neutral/loss
Side effects	Low/savings	Low
Psychosocial benefits	High	N/A

Source: Adapted and reprinted with permission from The American Diabetes Association. Copyright 2016 by the American Diabetes Association [28]

Employ Qualified Staff

Key to successful diabetes education is the method of delivery and engagement of each individual in their care. The focus of diabetes education is to address the clinical, psychosocial, and behavioral needs of individuals. Historically, preparation of educators has been more focused on teaching them facts about diabetes rather than emphasizing principles of behavior change. Clinicians who commit to offering diabetes education and support require a unique blend of the art and science of diabetes care and resources to meet the needs of each individual to ensure a flexible, person-centered approach is taken.

The diabetes educator's role was developed to address the scope of diabetes self-management education and support needs of individuals with diabetes. In the United States, the Certified Diabetes Care and Education Specialist credential identifies those who meet specific knowledge and practice

criteria related to diabetes education [23]. A Certified Diabetes Care and Education Specialist may be a nurse, dietitian, pharmacist, social worker, psychologist, nurse practitioner, or other clinician. Different clinics in different locations around the world address the coordination and offering of diabetes education and support in various ways. Research highlights the value of a team-based approach to providing diabetes education; thus, the inclusion of a Certified Diabetes Care and Education Specialist or designated diabetes educator on the typical health care team is recommended to provide and/or coordinate diabetes education [5, 16].

With this in mind, clinical teams can plan how they address the ever increasing incidence of diabetes and corresponding need for specialized staff to educate those with diabetes. In the United States, there are over 19,500 Certified Diabetes Care and Education Specialists [30]. With over 34 million people in the United States having diabetes [31], each Certified Diabetes Care and Education Specialist would be responsible for the education needs of more than 1745 people. Worldwide, this lack of diabetes educators is likely even more staggering and highlights the need for increased preparation for diabetes educators and other clinicians who accept the responsibility of addressing the initial and ongoing education and support needs of individuals with diabetes.

Ensure Ongoing Access

To address the diabetes education and support needs of people with diabetes, the clinical team can review the needs listed in Table 28.6 and assign staff to each topic. Through discussion and consideration of other resources, teams can identify how to meet the individual needs of patients. In the United States, a referral from a provider is necessary to access a formal diabetes education program. A list of credentialed education programs can be found at www.diabeteseducator.org/deap or www.diabetes.org/erp. In other countries, national diabetes organizations typically list available resources. For example, Diabetes UK lists several nationally recognized diabetes education programs for type 1 and type 2 diabetes such as DESMOND, DAFNE, X-PERT, and Aspire [32].

It is essential that providers advocate for the education and support needs of their patients. Patients may not be aware of the value and outcomes associated with diabetes education, and some may not understand its necessity in addition to medication that they take. It is especially important to highlight the ongoing need for diabetes education and support throughout one's lifetime, including when other complicating factors influence diabetes care and when transitions in life and care occur. It may be easy to become distracted or focused on a new situation, allowing diabetes care to suffer and become a greater burden on the patient. Diabetes education does not occur in a single session; rather it is an ongoing collaboration with the diabetes team. Lack of follow-up can diminish previous behavior change and successes.

Communication among staff is critical whether or not the team is utilizing the services of a designated, formal diabetes education program. A continuous review of responsibilities, challenges, and successes can lead to many positive outcomes.

Who Are the Diabetes Educators?

The diabetes self-management education and support staff may be a team of professionals representing multiple disciplines, or it may include just one discipline. Often, the location and size of the organization determine the size of the leadership and education team. Members of the health-care team can contribute to an effective diabetes self-management education and support program by collaborating and providing clear communication [16].

In the United States, the Association of Diabetes Care and Education Specialists currently has over 12,000 members and represents multiple disciplines [33]. Diabetes education certification was first granted in 1986, and there are currently 46% RNs, including advanced practice nurses, 43% RDs/RDNs, and 8% RPhs certified in the United States [30]. Diabetes education is often considered a "specialty" or "specialization"; however, it is not considered its own profession or discipline. Diabetes educators are prepared in their specific discipline and often land in the specialty serendipitously.

Diabetes educators originally assumed this role "on the job"—seeing and responding to a need. Today, the need for diabetes education is greater than ever, and there are multiple paths to becoming a diabetes educator. Several universities have certificates and specialties in diabetes [34]. Continuing education is available on diabetes topics through several universities and organizations around the world. There are also national and international meetings where people can learn about diabetes education topics (see Table 28.7).

Diabetes education can range from minimal teaching in a primary or other care provider's office to formal education with a written curriculum and multiple follow-up visits, and anything in between. Health-care professionals may serve roles separate from or in addition to diabetes education.

Table 28.7 Preparation for diabetes educators

Name of program	Type of preparation	Organization/school	Website
Career Path Certificate Program	Training for health-care providers in the delivery of diabetes self-management education and support	Association of Diabetes Care and Education Specialists	https://www.diabeteseducator.org/education-career/career-path-certificate
Diabetes Essentials for Clinicians Diabetes Essentials for Non-Clinicians	Certificate programs	Benerd College; University of the Pacific	https://education.pacific.edu/education/professional-development/certificate-programs/diabetes-essentials-certificate-program
Diabetes Certificate	Diabetes certificate for undergraduate and graduate students	Ohio University	https://www.ohio.edu/chsp/ahsw/diabetes-certificate
Diabetes Education Certificate Course	Continuing education	Emory University School of Medicine	http://medicine.emory.edu/endocrinology/diabetes-education/diabetes-educator-certification.html
Diabetes Network for Health Professionals	Discussion, library, education	International Diabetes Federation	https://dnet.idf.org/en/
Diabetes Management Program	Certificate	University of Southern Indiana	https://www.usi.edu/health/center-for-health-professions-lifelong-learning/certificate-programs/diabetes-management-program/
Diabetes Concentration	Master of Science in Nursing students	UCSF	https://nursing.ucsf.edu/academics/programs/master-science-advanced-practice-programs/diabetes-concentration
Diabetes Educator Graduate Certificate Program	Continuing education	The Michener Institute	http://michener.ca/ce_course/diabetes-educator-graduate-certificate-program-2/
Diabetes Concentration	Pharmacy students	Drake University College of Pharmacy & Health Sciences	https://www.drake.edu/pharmacy/dualdegreesconcentrations/diabetesconcentration/
Diabetes	Postgraduate Certificate Postgraduate Diploma Postgraduate Master's	University of Leicester	https://le.ac.uk/courses/diabetes-msc-dl/2021
Peers for Progress	Seminars, videos, articles	University of North Carolina	http://peersforprogress.org/pfp-presentations/
Diabetes	Postgraduate Certificate Postgraduate Diploma Postgraduate Master's	Warwick Medical School	https://warwick.ac.uk/fac/sci/med/study/cpd/diabetes/
Diabetes Care Concentration	Master of Science in Nursing	Yale University School of Nursing	http://nursing.yale.edu/academics/master-science-nursing/masters-program-concentrations/diabetes-care-concentration
Diabetes	MSc and Postgraduate Diploma	University of South Wales	https://www.diabetes.org.uk/professionals/training%2D%2Dcompetencies/courses/pgdip-and-msc-in-diabetes%2D%2D-university-of-south-wales
Diabetes	MSc in Diabetes	Cardiff University	https://www.cardiff.ac.uk/study/postgraduate/taught/courses/course/diabetes-msc

Developing a Diabetes Education Program

Diabetes education takes place in a variety of practice settings, including the hospital, clinic, private practice, retail, community, and in virtual tele-health (or e-health) settings. There are no limits to where diabetes education can occur.

A needs assessment is a critical first step in developing or improving a diabetes self-management education and support program in any setting [12, 35]. (National Standards, 2022). Needs assessments ensure that the education program is effective and appropriate for the target population. Considerations may include age, culture, location, transportation, staffing, time of classes, length of classes, materials, cost, and other resources. It is important to determine at the outset the philosophy or mission of the program, as well as goals and objectives. Making goals measurable allows the program to be evaluated according to goal achievement.

Major organizations have established guidelines for developing, implementing, evaluating, and maintaining diabetes self-management education and support programs that meet high standards. In the United States, the American Diabetes Association oversees the Education Recognition Program [36], and the Association of Diabetes Care and Education Specialists oversees the Diabetes Education Accreditation Program [37].

Strategies for Successful Diabetes Education

While it is ideal to have access to a diabetes educator, that may not always be possible. Physicians and other team members often find themselves having to conduct or lead diabetes education for their patients. Consider the following eight tips to improve patient education and behavior change.

Collaborate with Patients

Engaging patients in their diabetes care plan makes the physician's job easier. When patients actively participate by thinking through and choosing treatment strategies—sharing in the decision of which medicine to take or selecting strategies to lose weight—they are more likely to follow through with behavior changes. Recognize that while the physician is the expert in diabetes care, the patient is the expert in his or her own diabetes and life. Collaboration between patient and provider is essential when designing a treatment plan for long-term success.

Ask Rather than Tell

Even though time is very limited in a medical visit, the physician can usually learn more about the patient's key concerns or possible barriers to treatment by asking open-ended questions such as, "What has been the hardest part about managing your diabetes since your last visit?" or "What questions do you have about your diabetes?" or "Many people have difficulty taking their medicine as prescribed. How often in the last week did you remember to take it?" When it comes to providing information about topics such as diabetes-related behaviors, ask the patient what they *can* do instead of telling them what they *should* do.

Recognize that Words Matter

Diabetes is often associated with stigma, shame, and guilt. The words commonly used in the language of diabetes care can accentuate negative feelings [38]. Frame messages to patients in a positive, hopeful manner. Use strengths-based language focusing on what patients do well ("tell me what you do to keep your numbers in target" instead of "what are you doing that gives you so many high blood glucose levels?"). Avoid judgmental, negative words and phrases such as "your diet *failed* to bring down your blood glucose…" or "your blood glucose numbers are not good." Instead, focus on the facts and physiology by saying, "Your glucose level is still elevated. This could be due to a decline in beta cell function. They are the cells that make insulin" or "Your most recent A1C is 9.2%. This is above the recommended goal of 7%" [39, 40].

Gather Educational Resources

Look for teaching aids that are best suited to the educational levels, languages, and literacy needs of your population. While printed handouts may be a common type of teaching aid, remember that the most useful handout might be a blank sheet of paper on which the key messages are written (or drawn) and specifically tailored for that patient. Enlist the help of others in your office to collect additional resources for use in demonstrations: food models, or nutrition fact labels; and diabetes supplies such as insulin pens, glucose meters, and hypoglycemia treatment options.

Provide a Written Care Plan

Provide each patient with a written care plan including instructions on how and when to monitor glucose, agreed upon targets, behavioral goals, and action steps as well as any medication changes. Record the results of the patient's blood pressure, weight, and lab tests to help them become familiar with their own biomarkers, know their targets, and recognize what medications and actions help to bring them into the target range.

Identify Resources

Network with diabetes educators. Even if they are not close by, there may be some who are willing to provide phone consultation or teaching for your staff. Talk with representatives from diabetes pharmaceutical, device, and technology companies as they will likely be able to identify educator experts. Learn about diabetes programs or services that may be helpful to your patients, such as diabetes support groups, education programs, community walking groups, and weight management programs.

Use the Teach Back Technique

It is common for patients to forget what they've been taught, even minutes after leaving the health-care provider's office. In addition to giving them something in writing, ask the patient, "Let's review what we went over. Can you tell me the key points of what you're going to do?" or "Show me how you're going to dial up the insulin dose on your pen and where you will give your first injection." Asking for a "teach back" helps identify misunderstandings of key points prior to the person leaving the office.

Mentor Others

If accessing a diabetes educator is not a realistic possibility, consider mentoring a nurse, medical assistant, or other office employee to be a "diabetes champion." Diabetes champions could also be people living with diabetes (even patients from your office) who are successfully managing their diabetes and have been taught specific guidelines for talking with other patients. Diabetes champions can help busy physicians by obtaining and organizing teaching materials and product samples, locating and listing community resources, and providing patients with accurate information about basic topics. Such topics could include healthy eating using the plate method, tips to increase physical activity, or strategies to remember to take medicines. Using teaching aids, such as a handout or a flipchart containing scripted messages, can help ensure that key points are made consistently and that the diabetes champion does not exceed his or her scope of practice. Using office staff in this way can have a powerful impact on improving diabetes care and providing busy physicians more time to spend with other patients [41].

Examples of Diabetes Education Initiatives Around the Globe

Increasing the Role of the Pharmacist in Community Education in Saudi Arabia

The Middle East is one of the regions where diabetes is escalating most rapidly. In the Kingdom of Saudi Arabia (KSA), the prevalence has jumped from 4.3% to 13.4% in the last 30 years. Over 50% of individuals over the age of 65 have diabetes [42]. While the role of the diabetes nurse and dietitian educators is increasing, the supply is not keeping up with the demand. Taking a cue from initiatives in other parts of the world, including the United States, where retail pharmacists have been taking on greater roles in diabetes education, the Nadhi Medical Company started a program to teach Diabetes Consultant Pharmacists (DCPs) to do in-store diabetes education. A program, "Let's Talk About Diabetes," which included four short, structured lessons on topics including taking medicines and monitoring blood glucose, was developed in a collaborative partnership with Joslin Diabetes Center and under the supervision of the KSA Ministry of Health. The program started as a pilot in 11 stores in 4 different cities and has expanded to over 40 stores. Numerous beneficial outcomes have been reported including an increase in medication taking behaviors (with 54% reporting not taking medicines as prescribed over past 7 days at baseline to only 14% reporting this at follow up) to an increase in those reporting using a meal plan to help manage their diabetes (from 6% to 32%). There were 380 customers with paired A1C results, which demonstrated a reduction from 8.5% (69 mmol/mol) to 7.32% (56 mmol/mol) ($p < 0.001$) [43]. As demonstrated by this project, community pharmacists in the retail setting can play an important and effective role in diabetes education.

Using Conversation Maps® to Facilitate Education in Pakistan

Diabetes education in group settings can be very effective. Research shows participants enjoy the group interaction and also demonstrate improvements in clinical outcomes (A1C). In addition, group education programs are cost effective [44]. Conversation Maps are a set of large, colorful images or pictorial guides, designed to engage small groups of people in discussion about their diabetes. Through the discussions, facilitated by a health-care professional, people not only learn about diabetes but also discuss their beliefs, clarify misconceptions, and share their personal stories of successes and challenges, thus learning from each other. Conversation Maps have been translated into 35 languages and are available in 110 countries. A study of 172 individuals in Pakistan participating in Diabetes Conversation Maps sessions found a high level of satisfaction with this teaching method with 72% preferring the group method using the maps over individual education. The study also demonstrated a large increase in individuals reporting willingness to make a change in behaviors to improve diabetes outcomes (from 20% at baseline to 66% after the class discussions) [45].

Using Community Health Workers in Diabetes Education and Prevention in Rural India

Recognizing the limited availability of diabetes educators, especially in rural areas, trained community health workers or peer counselors can be an effective resource and has been effectively demonstrated in India. In two different interventions, community health workers were taught by a diabetes educator to provide lifestyle education aimed at reducing risks for diabetes. Dietary education focused on improving the intake of fiber and protein from low-cost resources such as nutritionally rich drumstick leaves, millets, lentils, and whole grains. Educators emphasized avoidance of sweetened drinks, and nutrition teaching methods included cooking demonstrations, recipe competitions, and model meals. Community health workers promoted and reinforced physical activity with demonstrations, competitive fun events, and dancercise events for the younger respondents. Stress relaxation instruction included the importance of meditation and breathing exercises (familiar to many of the respondents). A Certified Diabetes Educator provided individual education and counseling for blood glucose management to a high-risk group. Interventions showed improvement in obesity and diabetes-related parameters and dietary intake [46]. As the need for diabetes educators grows, the use of community health workers is an effective and recommended option. The Association of Diabetes Educators Practice Synopsis on Community Health Workers suggests roles and competencies and offers recommendations for practice [47]. The Peers for Progress website offers many examples of successful interventions and resources available for training [48].

Engaging Group Activities for Support in Japan

Activities that bring people with diabetes together, such as support groups, have long been recognized as being helpful, and the Education Center of Kenichi Yamada Internal Medicine Clinic in Sendai, Japan has successfully initiated several innovative approaches. The clinic is designed as a very warm and welcoming space and even includes an art gallery displaying paintings from a local artist. The clinic's motto, "Hand-in-hand we think and take steps together," reflects their philosophy of the importance of partnership between the patient and provider. Their clinic website shows how diabetes education activities go beyond traditional classes, by including walking groups, concerts (offered along with diabetes education), cooking classes (where everyone participates), and classes with custom-tailored conversation maps. Activities such as these build community and support between participants and their health care providers [49].

Online Diabetes Educator Preparation: Certificate and Degree Programs

As the need for diabetes educators increases, different groups have implemented solutions to increase access to instruction programs. For example, the International Diabetes Federation offers a variety of classes in English and Spanish for diabetes educators through its "School of Diabetes." In addition, the Association of Diabetes Care and Education Specialists has several certificate courses available in English [50] Table 28.6 provides a partial list of academic and continuing education opportunities in diabetes. An Internet search can also identify the most current programs available.

Additional Roles for the Diabetes Educator

Diabetes educators are often called on for their expertise. Their presence and participation in social media is growing; there are more and more virtual chats and other opportunities for diabetes educators to share their experience and knowledge. Diabetes educators are also considered thought leaders in the field and are often asked to contribute to papers, meetings, and advisory boards. In addition, diabetes educators are being asked to serve as content experts for published materials. National organizations often ask diabetes educators to serve on committees and lend their expertise to special projects.

In addition, in a systematic review that looked at strategies for improving outcomes in type 2 diabetes, the authors concluded that the diabetes educator has a very important role. The most effective approaches to mitigating therapeutic inertia and improving A1C were those that empowered non-physician providers (such as diabetes educators and pharmacists) to initiate and intensify treatment independently, supported by appropriate guidelines [51].

Diabetes education is still in its early stages around the world, and diabetes educators have an opportunity to grow this specialty. While there are currently not enough diabetes educators to serve all people with diabetes, they can prepare diabetes paraprofessionals to help meet patients' education needs; they can partner with other professionals and encourage more people to become diabetes educators. Diabetes educators are leaders in using and teaching about mobile apps for diabetes management. They know how to interact successfully with people of all ages and generations. Diabetes educators recognize the value of diabetes technology and are teaching others how to use it. There is a possible role for diabetes educators in retinal screening, which could increase the number of people who have dilated eye exams each year and in turn get referred for care as needed [52].

It is impossible to predict what the future will hold for diabetes educators. The need for well-prepared diabetes educators is unrelenting. The opportunities for online education resources are increasing every day. Diabetes educators are well positioned to oversee that work and ensure timely, relevant, consistent, and accurate information is made available to people with diabetes and their loved ones.

Multiple Choice Questions

Which of the following have been found to improve as a result of diabetes self-management education?

1. A1C
2. Quality of life
3. Self-care behaviors
4. **All of the above**

According to the DAWN2 study, which of the following statements is true?

1. **About 50% of people report diabetes has a negative impact on their emotional well-being**.
2. About 25% of people report experiencing diabetes-related distress.
3. About 15% of people who attended diabetes classes reported no improvement.
4. All of the above.

What are considered the critical times for diabetes education?

1. At diagnosis and within the first 18 months
2. At diagnosis, when A1C is elevated, when insulin is initiated
3. **At diagnosis, annually and/or when not meeting treatment targets, when complicating factors develop, when transitions in life and care occur**
4. At diagnosis, when new medications are started, after a hospitalization

Diabetes self-management education and support can be provided by

1. nurse
2. dietitian
3. pharmacist
4. **all of the above plus others**

Content areas for diabetes self-management education and support include

1. healthy eating, exercise, medications, and monitoring
2. pathophysiology, treatment, and acute and chronic complications
3. healthy coping and problem solving
4. **all of the above**

If a Certified Diabetes Educator is not available, the following people are most qualified to provide diabetes education

1. physicians
2. family members
3. peer educators or community health workers
4. **1 and 3**

For professionals, ongoing preparation in diabetes education and support topics is available through

1. informal get-togethers with colleagues
2. **online academic degree programs and continuing education**
3. YouTube videos about diabetes
4. working with patients

Words and messages are important in diabetes. Recommendations for effective communication include using

1. strengths-based language
2. empowering language
3. language based on facts and physiology
4. **all of the above**

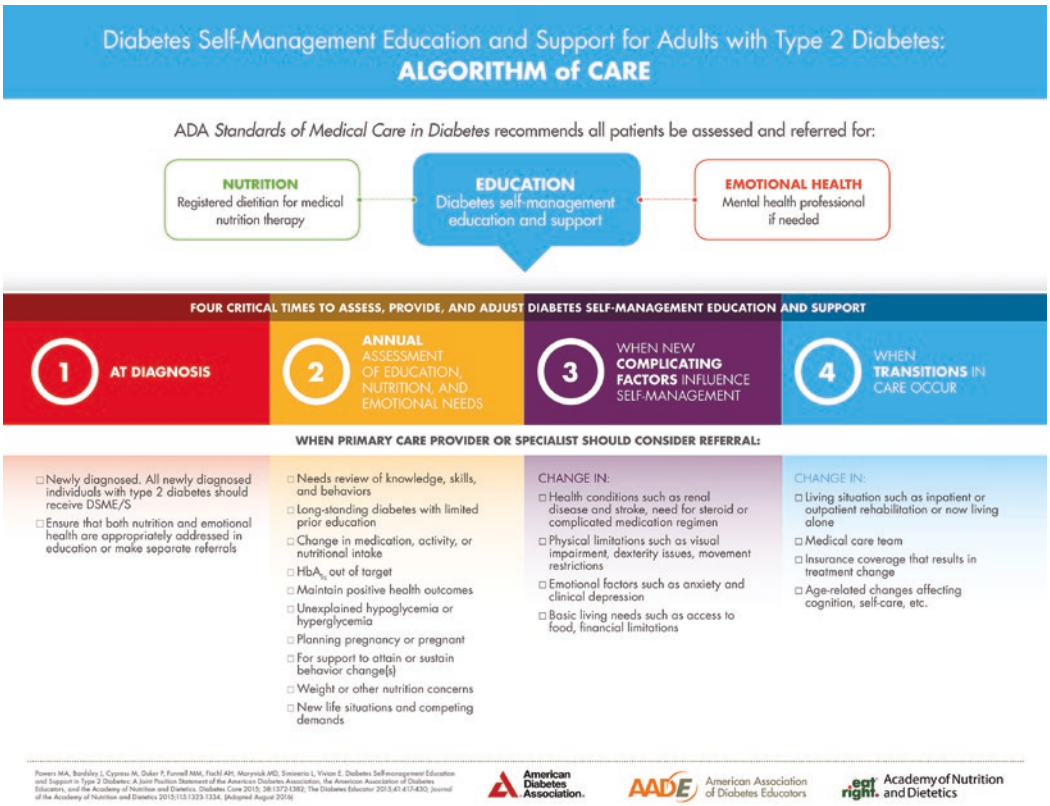
Successful strategies for diabetes education include

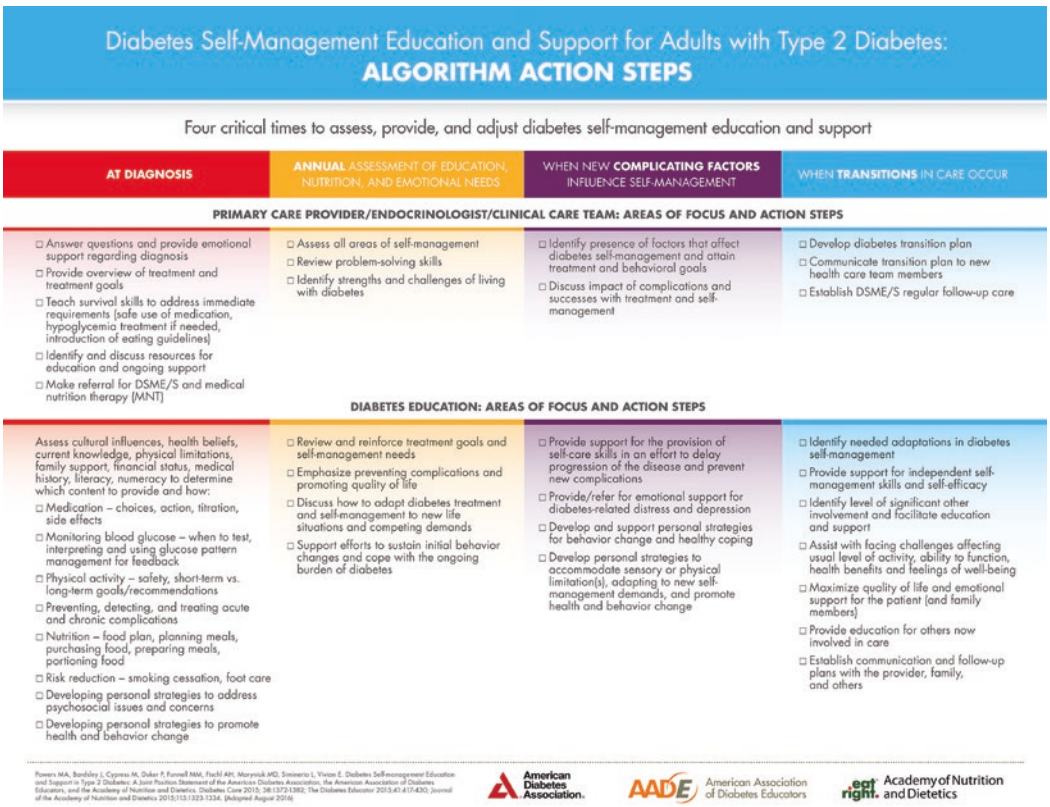
1. telling people what to do
2. giving people information, sending them home, and hoping for the best
3. **using the teach back technique**
4. people have enough to think about, they do not need written handouts

The most important sign of a successful diabetes education program is

1. lots of money coming in
2. **engaged patients**
3. lower A1C numbers
4. decreased incidence of hypoglycemia

Appendix


Diabetes Self-Management Education and Support for Adults with Type 2 Diabetes:
ALGORITHM of CARE
ADA Standards of Medical Care in Diabetes recommends all patients be assessed and referred for:
NUTRITION
Registered dietitian for medical nutrition therapy
EDUCATION
Diabetes self-management education and support
EMOTIONAL HEALTH
Mental health professional if needed
FOUR CRITICAL TIMES TO ASSESS, PROVIDE, AND ADJUST DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT
1 AT DIAGNOSIS
2 ANNUAL ASSESSMENT OF EDUCATION, NUTRITION, AND EMOTIONAL NEEDS
3 WHEN NEW COMPLICATING FACTORS INFLUENCE SELF-MANAGEMENT
4 WHEN TRANSITIONS IN CARE OCCUR
WHEN PRIMARY CARE PROVIDER OR SPECIALIST SHOULD CONSIDER REFERRAL:
Newly diagnosed. All newly diagnosed individuals with type 2 diabetes should receive DSME/S
Ensure that both nutrition and emotional health are appropriately addressed in education or make separate referrals
Needs review of knowledge, skills, and behaviors
Long-standing diabetes with limited prior education
Change in medication, activity, or nutritional intake
HbA1c out of target
Maintain positive health outcomes
Unexplained hypoglycemia or hyperglycemia
Planning pregnancy or pregnant
For support to attain or sustain behavior change(s)
Weight or other nutrition concerns
New life situations and competing demands
CHANGE IN:
Health conditions such as renal disease and stroke, need for steroid or complicated medication regimen
Physical limitations such as visual impairment, dexterity issues, movement restrictions
Emotional factors such as anxiety and clinical depression
Basic living needs such as access to food, financial limitations
CHANGE IN:
Living situation such as inpatient or outpatient rehabilitation or now living alone
Medical care team
Insurance coverage that results in treatment change
Age-related changes affecting cognition, self-care, etc.
American Diabetes Association.
AADE American Association of Diabetes Educators
eat right. Academy of Nutrition and Dietetics


Diabetes Self-Management Education and Support for Adults with Type 2 Diabetes:
ALGORITHM ACTION STEPS
Four critical times to assess, provide, and adjust diabetes self-management education and support
AT DIAGNOSIS
ANNUAL ASSESSMENT OF EDUCATION, NUTRITION, AND EMOTIONAL NEEDS
WHEN NEW COMPLICATING FACTORS INFLUENCE SELF-MANAGEMENT
WHEN TRANSITIONS IN CARE OCCUR
PRIMARY CARE PROVIDER/ENDOCRINOLOGIST/CLINICAL CARE TEAM: AREAS OF FOCUS AND ACTION STEPS
Answer questions and provide emotional support regarding diagnosis
Provide overview of treatment and treatment goals
Teach survival skills to address immediate requirements (safe use of medication, hypoglycemia treatment if needed, introduction of eating guidelines)
Identify and discuss resources for education and ongoing support
Make referral for DSME/S and medical nutrition therapy (MNT)
Assess all areas of self-management
Review problem-solving skills
Identify strengths and challenges of living with diabetes
Identify presence of factors that affect diabetes self-management and attain treatment and behavioral goals
Discuss impact of complications and successes with treatment and self-management
Develop diabetes transition plan
Communicate transition plan to new health care team members
Establish DSME/S regular follow-up care
DIABETES EDUCATION: AREAS OF FOCUS AND ACTION STEPS
Assess cultural influences, health beliefs, current knowledge, physical limitations, family support, financial status, medical history, literacy, numeracy to determine which content to provide and how:
Medication – choices, action, titration, side effects
Monitoring blood glucose – when to test, interpreting and using glucose pattern management for feedback
Physical activity – safety, short-term vs. long-term goals/recommendations
Preventing, detecting, and treating acute and chronic complications
Nutrition – food plan, planning meals, purchasing food, preparing meals, portioning food
Risk reduction – smoking cessation, foot care
Developing personal strategies to address psychosocial issues and concerns
Developing personal strategies to promote health and behavior change
Review and reinforce treatment goals and self-management needs
Emphasize preventing complications and promoting quality of life
Discuss how to adapt diabetes treatment and self-management to new life situations and competing demands
Support efforts to sustain initial behavior changes and cope with the ongoing burden of diabetes
Provide support for the provision of self-care skills in an effort to delay progression of the disease and prevent new complications
Provide/refer for emotional support for diabetes-related distress and depression
Develop and support personal strategies for behavior change and healthy coping
Develop personal strategies to accommodate sensory or physical limitation(s), adapting to new self-management demands, and promote health and behavior change
Identify needed adaptations in diabetes self-management
Provide support for independent self-management skills and self-efficacy
Identify level of significant other involvement and facilitate education and support
Assist with facing challenges affecting usual level of activity, ability to function, health benefits and feelings of well-being
Maximize quality of life and emotional support for the patient (and family members)
Provide education for others now involved in care
Establish communication and follow-up plans with the provider, family, and others
American Diabetes Association.
AADE American Association of Diabetes Educators
eat right. Academy of Nutrition and Dietetics

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Diabetes and Mental Health: From Distress to Depression

29

Gerhard Heinze-Martin, Diana Patricia Guizar, and Napoleon Andrés Bernard

Introduction

The comorbidity between depression and diabetes mellitus was recognized by the British physician Thomas Willis in the seventeenth century; he noted that diabetes frequently appeared in individuals who had previous experiences of stress in their lives, "diabetes is a consequence of prolonged sorrow" [1, 2].

Diabetes mellitus (DM) prevalence is increasing worldwide; the World Health Organization predicts there will be 300 million people having this disease by 2025, and due to an increase in prevalence, diabetes has become an epidemic throughout the world and one of the leading causes of death, affecting approximately 422 million people globally. Depression is a frequent comorbidity of both type 1 (T1D) and type 2 diabetes (T2D) [3, 4]. The high prevalence of the comorbidity worldwide is characterized by high morbidity and mortality in patients who suffer from both diseases [5, 6]. Also, WHO reveals that 49% of the depressed people with type 2 diabetes mellitus (DM2) were misrecognized by the primary-care system. The comorbidity between diabetes mellitus and depression is a serious chronic conditions that negatively affects the quality of life, increase functional disability, and reduce life expectancy [7, 8]. The comorbidity represents a major clinical challenge as the outcomes of each condition are worsened by the presence of the other. Today, we know that people with type 1 diabetes mellitus (DM1) and DM2 have an increased risk of developing depressive symptoms, and people with depression also have an increased risk of developing diabetes [9]. However, the exact mechanisms through which these two conditions affect each other remain uncertain, and there are few integrated approaches to the problem. The American Diabetes Association recommends diabetes screening every 3 years in all subjects above 45 years of age; an earlier and more intensive testing is advised in overweight persons with other risk factors (physical inactivity, family history of diabetes, previous gestational diabetes, hypertension, hypertriglyceridemia, polycystic ovary syndrome). Depression disorder should be included among the risk factors that should drive diabetes screening [10]. There is also evidence that suggests diabetes mellitus is associated with a higher frequency of suicide, with depression being the most commonly reported psychiatric disorder in patients with diabetes who attempted suicide [11].

Definitions

- *Major Depressive Disorder.* According to the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) [12] and the tenth revision of the International Classification of Diseases (ICD-10) [13], major depressive disorder is a mood disorder, made on the basis of several symptoms and the extent of functional deterioration. The diagnosis according to DSM-5 is made when at least five of nine symptoms (feelings of guilt or worthlessness, fatigue or loss of energy, concentration problems, suicidality or thoughts about death, change in weight, change in activity, change in sleep), including a minimum of one core symptom (a diminished or irritable mood, decreased interest or pleasure), lasts at least 2 weeks. The different possible combinations of depression symptoms all leading to a diagnosis are large and result in various clinical profiles of depression.

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- *Distress.* The term was introduced by Hans Selye in the early 1970s; he distinguished between stress initiated by negative, unpleasant stressors (distress) and positive stress (eustress) [14] Ridner defined it as "the unique discomforting, emotional state experienced by an individual in response to a specific stressor or demand that results in harm (irritability, fear, nervousness, and sadness), either temporary or permanent to the person" [15].
- *Diabetes distress* is an emotional distress that stems from a variety of areas related to living with the burden of a chronic illness [16]. Living with diabetes can be complex, demanding, and sometimes confusing. Patients often feel frustrated, angry, overwhelmed, and/or discouraged. When the challenges of caring for diabetes affect the individual on an emotional level, it may result in diabetes-related distress [17].

Epidemiology of Comorbid Depression–Diabetes

In 2015, the prevalence of diabetes worldwide was of 1 in 11 adults, and the estimated prevalence of the impaired glucose toleration was of 1 in 15 adults. These numbers are expected to further increase, especially in the urban population, leading to more medical and economic challenges, added on top of the 12% global health expenditure currently spent on diabetes [18]. Depression is a common and serious disease with a lifetime prevalence from 11% to 15% [19]. Depression and anxiety are the fourth cause, while diabetes is the eighth cause of disability adjusted life years (DALYS) in developed countries [20]. A common cited meta-analysis (including type 1 and type 2 diabetes) showed that the overall odds of depression was twice as high for people with diabetes compared to nondiabetic controls and no significant differences in prevalence were found between these two types of diabetes [21]. Few years later, Ali and colleagues realized a meta-analysis of ten controlled studies focusing on type 2 diabetes; the prevalence rate of depression was found higher in people with diabetes compared to controls. Barnard [22] published a systematic review of four controlled studies which reported that the prevalence of clinical depression was 12.0% for people with type 1 diabetes compared to 3.2% in people without diabetes. Moussavi and colleagues [23] carried out a survey in 60 countries and found that the self-reported 1-year prevalence of depressive symptoms in diabetes was 9.3% compared to 3.2% in people without a comorbid condition. Studies indicate that during the period following the diagnosis of type 2 diabetes, important changes occur that are likely to be associated with the development of depression. Skinner and colleagues [24] found that the prevalence of depression was not significantly different from a normative sample in the first year after diagnosis, although a significant number of people had persistent depressive symptoms during that year. Use of antidepressant medication was also increased temporarily during the first year after diagnosis of type 2 diabetes [25].

Recently [26], the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), in collaboration with the National Institute of Mental Health and the Dialogue on Diabetes and Depression, concluded that the prevalence of this comorbidity varies considerably by method of depression assessment; for example, prevalence rates for elevated depressive symptoms range from 12% to 27% across studies of people with type 1 and type 2 diabetes, while rates of depressive disorders, as assessed by psychiatric interview protocols, range from 8% to 15% in adults with type 1 and type 2 diabetes [27]. Nouwen and colleagues [28] in a recent meta-analysis concluded that the incidence of depression is 24% higher in people with diabetes type 2, and the presence of 2 or more complications (neuropathy and nephropathy) is associated with a greater than two-fold increase in the risk of depression in people with type 2 diabetes.

Meurs and colleagues [29] found that depression was more prevalent in people with diabetes, regardless of the fact that they had diagnosed or undiagnosed diabetes ($n = 90{,}686$).

We can conclude that based on available epidemiological studies, diabetes is associated with increased risk of depression and in the same way a depressive disorder increase the risk of metabolic diseases like diabetes. In other words, there is a bidirectional association between diabetes and depression, a complex relation that might share biological mechanisms, whose understanding could provide a better treatment and avoid complications of comorbidity. In 2015, Berge et.al and Moulton et.al [30, 31] indicated three possible directions for the association of diabetes and depression: both diseases might have a common etiology, diabetes increasing the prevalence or risk for future depression and depression increasing the prevalence or risk for future diabetes.

Mechanisms Underlying the Association Diabetes–Distress–Depression (Fig. 29.1)

Depression was an understandable reaction to the difficulties resulting from living with a demanding and life-shortening chronic physical illness that is associated with chronic and debilitating complications. De Ridder and colleagues [32] found distress is prevalent in medical patients with chronic illness because it challenges their habitual coping strategies, with most eventually reaching good psychological adjustment, but for about 30%, the adjustment phase is long lasting or unsuccessful. In diabetes, distress presents in 10–30%, depending on case mix, and can differ across settings and

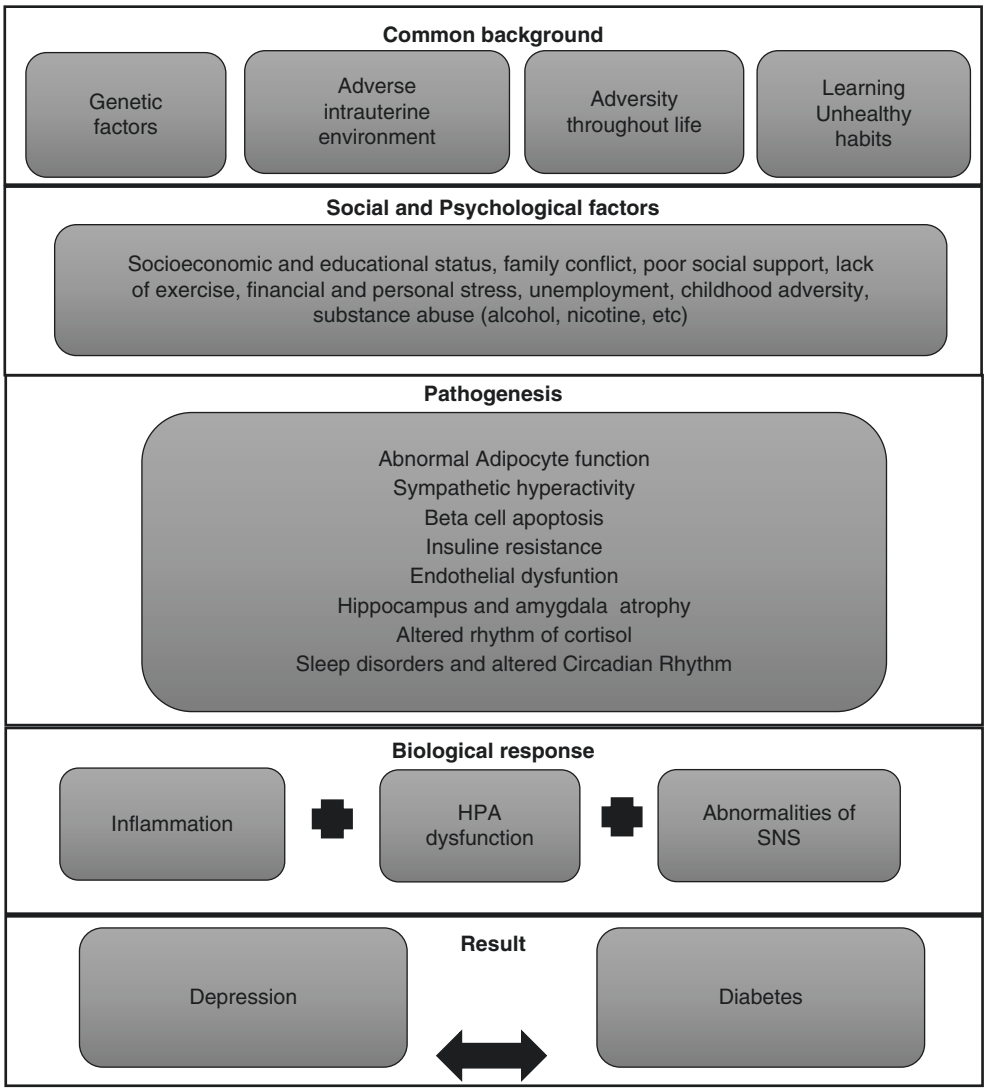

Fig. 29.1 Mechanisms underlying the association diabetes–distress–depression

countries [33]. In an observational study during 18 months in patients with type 2 diabetes in the USA, almost a third of the patients reported increased diabetes distress at least at one of three measurement timepoints, with 22% reporting high diabetes distress at all three measurement points [34]. Fisher and colleagues [35] consider emotional distress as a core, continuous dimension that underlies diabetes-related distress, subclinical depression, elevated depressive symptoms, and major depressive disorder.

Adherence to Treatment, Hygienic, and Dietetic Measures

Depression and type 2 diabetes share similar environmental and lifestyle risk factors, such as socioeconomic deprivation, social adversity, smoking, and reduced physical activity. Recent studies [33–39] showed that childhood adversity (abuse, deprivation, and neglect) and work stress have effects on depression and diabetes. Depression is associated to self-neglect and low self-esteem, which might increase risk of unhealthy lifestyles, for example, increased caloric intake, high body-mass index (BMI), poor diet, low levels of physical activity, and smoking, that generate metabolic changes and incremented the risk of Diabetes.

Lustman and colleagues [40] on a meta-analysis showed that depression in diabetes was associated with significantly worse glycemic control, although the effect size ($r = 0.17$) was small. For depression diagnosed by a standardized clinical interview, the effect size was larger ($r = 0.28$). Evidence suggests that diabetes-related distress, rather than depression, is associated with decreased glycemic control over time [41]. It is important to know that not all depressive symptoms are equally important. Nefs and colleagues [42] identified anhedonia as the strongest predictor for poor glycemic control, in contrast with Bot and colleagues [43] who identified depressed mood and somatic symptoms of depression

(sleeping difficulties, appetite problems, and psychomotor retardation) as best predictors.

The link between depression and type 2 diabetes is bidirectional: type 2 diabetes is associated with a roughly 20% increased risk of incident depression [44, 45], and depression is associated with a 60% increased risk of incident type 2 diabetes. A meta-analysis by Gonzalez and colleagues found that depression has a moderate to weak association with self-care behavior (overall r = 0·21) including missed medical appointments, diet, exercise, medication use, glucose monitoring, and foot care [46]. In a primary study, a 1-point increase in depressive symptoms scales was found to result in a 10% increased risk of nonadherence to fruit and vegetable intake and foot care. Findings of cross-sectional studies [41, 47] of the association depression–diabetes self-care showed that healthy eating, regular exercise, and low calorie intake and low-fat food showed a strong negative correlation with depressive symptoms and diabetes distress but not with the presence of clinical depression, which, according with Holt and colleagues [47], suggests the possibility that there may be a mutually reinforcing phenomenon that poorer adherence to self-care may increase blood glucose, which in turn may contribute to depressive symptoms and consequently contribute to decreased adherence to self-care behaviors.

The Hypothalamic-Pituitary Adrenal (HPA) Axis Dysfunction

Stress is a state of threatened homeostasis, evoking adaptive responses. As we already know, the major role of the HPA axis is to mediate the neuroendocrine stress response, in order to reestablish body homeostasis. As a brief reminder, the HPA axis, first corticotropin releasing factor (CRH) is synthesized by neurons in the parvocellular cell division of the paraventricular nucleus (PVN), and it is secreted into the pituitary portal blood and enters the anterior pituitary and binds to type 1 CRH cell-surface receptors, resulting in ACTH which acts on the adrenal cortex, to stimulate cortisol secretion. Cortisol inhibits the secretion of CRH and ACTH from the hypothalamus and anterior pituitary, respectively. Once cortisol is released from the adrenal cortex in response to ACTH stimulation, it functions to increase blood glucose levels through its action on glycogen, protein, and lipid metabolism [48, 49].

Chronic stress and cortisol excess can lead to:

(a) Increased portal and peripheral free fatty acids to be released into the circulation, which impairs the ability of insulin to translocate intracellular SLC2A4 glucose transporters to the cell surface and can, therefore, contribute to metabolic syndrome, insulin resistance, muscle weakness, hirsutism, increased bruisability, and type 2 diabetes [50]
(b) Accumulation of visceral fat by promoting differentiation and proliferation of adipocytes, redistributing fat from peripheral to central depots, and increasing the size and number of adipocytes [51]
(c) Hindered neurogenesis in the hippocampus and amygdala [52]
(d) Depression [53]

Several biological mechanisms have been proposed for the association between diabetes and depression throughout the life course. Gragnoli and colleagues [54] hypothesized that these biological mechanisms may reside at the level of CRH receptors which may carry genetic variants that determine protein dysfunctions responsible for HPA axis hyperactivation and for impaired cortisol-mediated feedback response in depression. The genetic variant at the level of CRHR1 that contributes to increased CRH levels in the hypothalamus may as a loss of function variant contribute to reduce insulin secretion in the pancreatic beta cell, which jointly to the prediabetic insulin-resistant state due to hypercortisolism, may lead to type 2 diabetes. In contrast, Horwath and colleagues [55] hypothesized that atypical depression is associated with a hypoactive HPA axis and hypocortisolism. However, patients with atypical depression also have insulin resistance possibly due to a noncortisol-mediated increase in visceral fat. These patients, in fact, have an increased food intake, especially carbohydrates, which may contribute to the decreased insulin sensitivity.

Conventional measures used to assess HPA axis activity showed in depression and diabetes elevated 24-hour urine free cortisol levels, failure to suppress cortisol with dexamethasone suppression test, adrenal gland enlargement, and performing the dexamethasone–corticotrophin-releasing hormone (CRH) test. The failure to suppress cortisol with the dexamethasone suppression test or the dexamethasone–CRH test suggests injury to the HPA axis a negative feedback loop and an inability of the HPA axis to appropriately terminate the stress response, resulting in excessive cortisol exposure.

Abnormalities of the Sympathetic Nervous System (SNS)

Carney and colleagues [56] documented elevated heart rate, lower heart rate variability, and high heart rate responses to physical stressors in depressed psychiatric patients compared with healthy controls. Few years later, Udupa and colleagues [57] found that depressed patients versus controls had higher low-frequency/high-frequency ratios and higher basal heart rates, suggesting a shift in SNS activity toward enhanced sympathetic tone. In a much larger study of Carol

and colleagues [58], they suggested that depression is associated with a blunted cardiovascular response to acute stress because they found that depressed patients were negatively associated with systolic blood pressure and heart rate reaction to paced auditory serial arithmetic testing after adjusting for gender, occupation, BMI, stress task performance score, medications (antidepressants and antihypertensives), and baseline cardiovascular activity.

Catecholamines are counterregulatory hormones that induce insulin resistance by acting on β3 receptors found in intra-abdominal and visceral fat and promotes lipolysis, leading to increased free fatty acid release [59]. A disease in which this mechanism is exemplified is pheochromocytoma (a rare neuroendocrine tumor involving overproduction of catecholamines), where insulin resistance, significant improvements in 24-hour urine catecholamine levels, fasting plasma glucose, and fasting insulin were notable features [60].

Inflammation and Innate Immunity

Depression

Studies in experimental animals and humans identified a close connection between the immune system and neurocircuits in the brain, which may have implications for the role of inflammation in the development of depression [61]. Two meta-analyses of cross-sectional studies [62, 63] provided evidence that patients with depression have higher circulating levels of biomarkers of subclinical inflammation, in particular C-reactive protein (CRP), interleukin (IL)-6, IL-1 receptor antagonist (IL-1ra), and tumor necrosis factor (TNF)-α, than nondepressed individuals. Stewart and colleagues [64] demonstrated that baseline depression scores and BMI were predictors of increase in IL-6, which suggests that depressive symptoms possibly precede and contribute to the inflammatory processes. Gimeno and colleagues [65] showed that baseline CRP and IL-6 were predictive of cognitive symptoms of depression. One year later, Weinstein and colleagues [66] found heightened acute mental stress reactivity in depressed individuals with higher IL-6, TNF-α, and CRP compared with controls; their results were supported by the meta-analysis of Dowlati and colleagues [67]. Recently, Khandaker and colleagues [68] found that increased concentrations of CRP and interleukin 6 predicted increased risk of depression.

Diabetes

Many studies support the association of inflammation and diabetes: Bretoni and colleagues [69] found higher CRP, IL-6, and fibrinogen levels; Aso and colleagues [70] found higher CRP, IL-6, and plasminogen activator inhibitor-1; Valle Gotlieb and colleagues [71] found higher high-sensitivity CRP (hs-CRP), oxidized low-density lipoprotein (LDL), oxidized LDL autoantibodies, and IL-6 among diabetic patients versus controls. Specifically, T2D and subclinical inflammation are linked in a bidirectional relationship [5]. The extent of chronic low-grade immune activation in T2D is exacerbated by the manifestation of macro- and microvascular complications during the progression of the disease [72]. The extent of chronic low-grade immune activation in T2D is exacerbated by the manifestation of macro- and microvascular complications during the progression of the disease [72]. It is currently not clear to what extent inflammatory processes mediate the increased risk of depression in patients with T2D. Furthermore, it remains unclear whether this association is independent of diabetic complications, which are highly prevalent in patients with longer diabetes duration. Additionally, it is not completely clarified whether associations between inflammation and depression are also present in patients with T1D. Both diabetes types share hyperglycaemia as the diagnostic criterion. However, they represent opposite ends of a continuum with different etiologies, which extends to the contribution of immune activation and inflammation [73].

Depression–Diabetes–Inflammation

Several studies proved that both depression and diabetes are associated with proinflammatory cytokines and elevation of inflammatory markers [74–78], specifically in type 2 diabetes, where raised concentrations of proinflammatory cytokines lead to pancreatic β-cell apoptosis and insulin resistance [79]. Epidemiological studies proposed innate immunity (interleukin 6 and CRP) as a possible mechanism by which depression and type 2 diabetes could develop as a result of stressors throughout the life course (abuse, neglect, or both before age 16 years, low socioeconomic status) [80]. Laake and colleagues [81] found that patients with newly diagnosed type 2 diabetes and depression were more overweight, younger, had higher concentrations of C-reactive protein (CRP) and interleukin 1-receptor antagonist and higher white-cell counts than those with type 2 diabetes who were not depressed.

Sounds logical that if inflammation is involved in pathogenesis of depression and type 2 diabetes, reduction in inflammation might be a novel treatment. Recent placebo-controlled trials with anti-inflammatory agents (interleukin 1 receptor antagonist and nonsteroidal anti-inflammatory drugs) found that they improve glycaemic control [82, 83]. However, there are no studies that have attempted to modify inflammation in treatment of depression in patients with type 2 diabetes.

Herder and colleagues [84] found that serum high-sensitivity C-reactive protein (hsCRP) and the ratio of high-molecular-weight (HMW)/total adiponectin were positively associated with depression symptoms evaluated by ADS-L

(Allgemeine Depressionsskala, Langversion) in T2D, but not in T1D. In contrast, serum levels of soluble intercellular adhesion molecule (sICAM)-1 were positively associated with ADS-L only in T1D. The latter association was significantly different between both diabetes types. No associations were observed for interleukin (IL)-6, IL-18, and soluble E-selectin. Only the association between HMW/total adiponectin and ADS-L in T2D remained significant after correction for multiple testing.

Circadian Rhythms

Sleep architecture variations can be seen before onset of depressive symptoms, suggesting that a subpopulation might be at increased risk of depressive symptoms and metabolic disturbances. Many studies found that disrupted sleep patterns (decreased slow-wave sleep and increased rapid eye movement density), sleep apnea, poor sleep quality, and altered circadian rhythms are associated with depression, obesity, insulin resistance, and type 2 diabetes [85, 86]. There is also an emerging biological pathway that proposes it could be changes in the expression of clock genes (genes that are associated with regulation of circadian rhythm), by environmental cues (light–dark cycles, food, glucose concentrations, social cues, antidepressant therapy) [87–89]. In patients with type 2 diabetes, clock gene expression has been directly associated with fasting glucose concentrations, and on depression, the rapid antidepressant actions of sleep deprivation therapy might be due to resetting of abnormal clock genes and subsequent restoration of circadian rhythms, although further studies are needed.

Antidepressant

A recent study regarding the association between the antidepressant use and the glycemic control showed that in adults with diabetes, the use of multiple antidepressant subclasses increased significantly the levels of Hb A1C, suggesting that antidepressive treatment may be a risk factor for suboptimal glycemic control [90]. Prior studies suggested that short-term antidepressive treatment of nondiabetic depressed patients has a beneficial effect and improves insulin sensitivity together with improving depression, but on the long run, the effects might be opposite [91]. Noradrenergic antidepressants are an exception and may lead to impaired insulin sensitivity even in nondiabetic patients [91]. Selective serotonin reuptake inhibitor treatment may improve the glycemic control in depressed DM2 patients and is the only class of antidepressants with confirmed favorable effects on glycemic control on both short- and long-term use [92]. Randomized controlled trials have emphasized that antidepressants vary considerably in their association with weight gain, and both hyperglycemic and hypoglycemic effects have been observed [93].

Future research should clarify the relation between baseline antidepressant use and development of prediabetes stages, and the extent to which antidepressant use has direct effects on diabetogenic pathways, rather than being a marker of depression itself.

Stage of Development

Childhood

Managing a chronic illness can be challenging, and developing effective coping strategies to overcome difficulties is essential for maintaining health, balance, and happiness. Type 1 diabetes is one of the most common chronic illnesses of childhood and requires a complex and demanding treatment regimen. While the large majority of childhood diabetes is type 1, there are increasing numbers of adolescents with type 2 diabetes who, requiring a similar treatment regimen, are subject to comparable risk factors for stress. Some aspects of diabetes management might be done by the children themselves, such as self-administration of insulin and attendance at regularly scheduled diabetes care appointments in clinics and hospitals. These aspects are demanding and can be disruptive and stressful, illustrating how children live with diabetes; the adult caregiver is mostly responsible for the complex decision-making associated with these tasks, such as dosing insulin on the basis of blood glucose readings and diet. Therefore, living with diabetes can feel overwhelming for parents and children because constant vigilance is required for proper care; the relation between depression and diabetes in childhood take into account both the child and their familial relationships [6].

Some evidence suggests that children with type 1 diabetes who grew up in an environment of high expressed emotion have poor glycemic control. Critical parenting behaviors increase depressive symptoms, with associated reduction of self-care behaviors [94]. Clinically, addition of structured behavioral group training has been shown to reduce parental stress and maintain improved glycemic control over time [95]. Children with diabetes experience higher rates of depression and other emotional problems than the general population. Recent studies suggest that children with both type of diabetes are at equal risk for psychological challenges. Depressive symptoms are particularly worrisome in youth with type 1 diabetes, given that on the lower end of risk these symptoms are related to poor self-care and on the higher end of risk are related to suboptimal glycemic care and even recurrent diabetes hospitalizations [96, 97].

Adolescence

Adolescence is a developmental stage during which youth are developing independence from parents, at the same time

that they are experiencing rapid biological and hormonal changes. Depression has been shown to interact adversely during transition from childhood to adolescence, maybe because of the increased independence and diabetes self-management, such as self-monitoring of blood glucose, dietary intake, and insulin dosing [98]. About 15–25% of adolescents with type 1 diabetes experience depression compared to 14.3% in children without a chronic illness, which translates into a rate two to three times found in the general adolescent population [99, 100]. This increased independence coincides with emergence of risk-taking behaviors, such as experimentation with tobacco and alcohol, and desire for peer approval. In view of these rapid psychological and physiological changes, diabetes-specific distress is well-characterized in adolescents with diabetes and is associated with poor glycemic control, prominent negative beliefs about diabetes, and reduced self-efficacy [101].

Adolescence is a key period for development of eating disorders, which are likewise associated with depression and the desire for peer approval. Adolescents with type 1 diabetes and disturbed eating behavior are far more likely to report depressive symptoms than those with type 1 diabetes alone, but do not consistently have poorer glycemic control, prospectively [102]. Recently, Corathers and colleagues [103] showed that high scores on the Children's Depression Inventory (CDI) were associated with decreased blood glucose monitoring frequency and increased HbA concentrations. However, Zduncyk and colleagues [104] found that the prevalence of depressive symptoms in patients with poor glycemic control was similar to those with good glycemic control. Further studies are needed for longitudinal assessment of potential benefits of depression screening on diabetes outcomes and to emphasize the apparent vulnerability of all adolescents.

Impact on Clinical Evolution and Quality of Life of Comorbid Diabetes–Depression

Diabetes produces structural changes in the brain—cerebral atrophy and lacunar infarcts—and blood flow changes of both hypo- and hyperperfusion [105]. Reductions in brain volumes restricted to the hippocampus were found in patients with diabetes, while an inverse relationship between glycemic control and hippocampal volume was present. HbA1C was described as the only significant predictor of hippocampal volume [106]. Similarly, depression is associated with neurodegenerative processes, especially at the level of the prefrontal cortex and hippocampus [107]. Severe hypoglycaemia in patients with DM2 and without antidepressive treatment was positively associated with the severity of depressive symptoms, independent of glycemic control, insulin therapy, lifestyle factors, and diabetic complications [108]. A meta-analysis estimating the association between depression and neuropathy in patients with DM2 could not clarify if the relationship is bidirectional or not. Many studies around the world demonstrates the relation between diabetes complications and depressive symptoms. Heinze and colleagues (in press, 2017) [109] presented a comparative cross-sectional study, with a systematic random sample of 206 DM2 patients (mean age 53.3 ± 8.21 years), of which 46 patients (22.3%) had depression (34 women and 12 men, mean age 52.0 ± 7.1 years). Depressed patients showed a lower mean in WHO-5 (Well-Being Index), greater discomfort on PAID (Problem Areas in Diabetes Questionnaire), and presented more complications of diabetes. Within which, neuropathy and retinopathy presented more frequently like complication. This study concluded that patients with comorbid DM2-depression showed a greater number of complications; two of which represent an impact on quality of life. Deschênes and colleagues [110] found that the number of diabetes complications at baseline was positively associated with a greater risk of elevated depressive symptoms, with the highest risk found for those with four to six complications at baseline. Cerebrovascular disease was the complication most strongly associated with incident depressive symptoms. Coronary artery disease, peripheral vascular disease, and neuropathy were also associated with the risk of depression, whereas foot problems and eye problems were not. Additionally, a greater number of diabetes complications was associated with recurrent/persistent depression, though with a small effect size. A parallel process latent growth curve model indicated that increases in diabetes complications were associated with increases in depressive symptoms during the course of the follow-up period.

Depression has a synergistic effect in patients with DM1 and DM2, increasing the risk for complications of both micro- and macro-vascular nature, increased hyperglycemia, predicting greater mortality. In older adults, the comorbidity also predicts an earlier incidence of complications [111]. Both diabetes and depression reduce the quality of life for an individual, but together they have a more negative impact [112]. Due to the negative effects on health, the rise in complications, both diseases should be recognized in an individual and treated simultaneously, in order to reduce depression and better control the diabetes. However, depression remains underdiagnosed and untreated in diabetic patients [113].

Implications for Research

There is a growing need to understand the similarities and differences between correlates of depressive symptoms, major depressive-disorder, and diabetes-specific distress (in both type of diabetes). Particularly in type 1 diabetes, further research is needed to identify risk factors and potential bio-

logical and cerebral correlates of depression, and in type 2 diabetes, further basic science research is need to identify the concurrent effects of biological processes and consistent neuroimaging correlates of the comorbidity diabetes–depression.

Multiple Choice Questions

1. What are the most frequent complications of type 2 diabetes in patients with depression?
   (a) Cerebrovascular disease and myocardial infarction
   (b) Myocardial infarction and macular edema
   (c) **Neuropathy and retinopathy**
   (d) Macular edema and retinopathy
   (e) Cerebrovascular incident and neuropathy

   Additional comment:
   The most frequently complications in type 2 diabetic patients with depression observed are neuropathy and retinopathy.

2. What are the mechanisms underlying the association diabetes–distress–sdpression?
   (a) Adherence to treatment and hygiene and dietetic measures
   (b) Hypothalamic-pituitary-adrenal axis dysfunction
   (c) Inflammation and Innate immunity
   (d) Abnormalities of the sympathetic nervous system
   (e) **All the answers are correct**

   Additional comment:
   The association diabetes–distress–depression is composed of many variables, including adherence to treatment and hygiene and dietetic measures, hypothalamic-pituitary-adrenal axis dysfunction, inflammation and Innate immunity, and abnormalities of the sympathetic nervous system.

3. What are the antidepressants that have a greater positive effect on glucose control?
   (a) **Selective serotonin reuptake inhibitors**
   (b) Tricyclic antidepressants
   (c) Serotonin-noradrenaline reuptake inhibitors
   (d) Monoamine-oxidase inhibitors
   (e) Norepinephrine-dopamine reuptake inhibitors

   Additional comment:
   Selective serotonin reuptake inhibitor treatment may improve the glycemic control in depressed DM2 patients and is the only class of antidepressants with confirmed favorable effects on glycemic control on both short- and long-term use.

4. Is depression associated with a neurodegenerative brain process, in which area has it been documented?
   (a) Hypothalamus and motor area
   (b) **Prefrontal cortex and hippocampus**
   (c) Occipital region and cerebellum
   (d) Cerebellum and hippocampus
   (e) Temporal and occipital area

   Additional comment:
   Diabetes produces structural changes in the brain—cerebral atrophy and lacunar infarcts— and blood flow changes of both hypo- and hyperperfusion. Depression is associated with neurodegenerative processes, especially at the level of the prefrontal cortex and hippocampus.

5. Patients with comorbidity: type 2 diabetes and depression present:
   (a) Less emotional complications
   (b) **Greater incidence in complications of type 2 diabetes**
   (c) Low self-esteem
   (d) Greater incidence in cardiac and renal alterations
   (e) High self-esteem

   Additional comment:
   Depression has a synergistic effect in patients with DM1 and DM2, increasing the risk for complications of both micro- and macrovascular nature, increasing hyperglycemia, and predicting greater mortality. In older adults, the comorbidity also predicts an earlier incidence of complications.

6. What is the fourth cause of disability adjusted life years (DALYS) in developed Countries?
   (a) Cancer
   (b) Type 2 Diabetes
   (c) **Depression and anxiety**
   (d) Bipolar disorder
   (e) Renal insufficiency

   Additional comment:
   Depression and anxiety are the fourth cause, while diabetes is the eighth cause of disability adjusted life years (DALYS) in developed countries.

7. Depressive symptoms increase the risk of:
   (a) **Diabetes mellitus**
   (b) Hepatic cirrhosis
   (c) Myocardial infarction
   (d) Macular edema
   (e) Cerebral infarction

   Additional comment:
   People with type 1 and type 2 diabetes mellitus have an increased risk of developing depressive symptoms, and people with depression also have an increased risk of developing diabetes.

8. Depression is associated to:
   (a) Increased caloric intake
   (b) Low levels of physical activity
   (c) Risk for developing diabetes
   (d) Worse glycemic control
   (e) **All the answers are correct**

Additional comment:

Depression is associated to self-neglect and low self-esteem, which might increase risk of unhealthy lifestyles, for example, increased caloric intake, high body-mass index (BMI), poor diet, low levels of physical activity and smoking, that generates metabolic changes and incremented the risk of diabetes.

9. Type 2 diabetes is associated with:
   (a) 0% of risk for developing depression
   (b) 10% of risk for developing depression
   (c) **20% of risk for developing depression**
   (d) 30% of risk for developing depression
   (e) 40% of risk for developing depression

Additional comment:

The link between depression and type 2 diabetes is bidirectional: type 2 diabetes is associated with a roughly 20% increased risk of incident depression [44, 45], and depression is associated with a 60% increased risk of incident type 2 diabetes.

10. The importance of establishing the diagnosis of comorbidity diabetes–depression is due to the statistics estimate that by the year 2015 the prevalence of diabetes mellitus will be:
    (a) 200 million people
    (b) **300 million people**
    (c) 400 million people
    (d) 500 million people
    (e) 600 million people

Additional comment:

Diabetes mellitus (DM) prevalence is increasing worldwide; the World Health Organization predicts there will be 300 million people having this disease by 2025, and due to an increase in prevalence, diabetes has become an epidemic throughout the world and one of the leading causes of death, affecting approximately 422 million people globally.

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Continuous Glucose Monitoring in Clinical Practice: Ambulatory Glucose Profile and the Application of Advanced Glucose Sensing Technologies to Clinical Decision-Making

Roger S. Mazze and Joel Rodriguez-Saldana

Introduction

Previous studies of subjects with normal glucose metabolism (at various ages and at risk for all forms of diabetes) have shown that normal glucose tolerance is characterized by glucose levels within a very narrow range (4–7 mmol/L) and in pregnancy by an even narrower range (3–6 mmol/L). Furthermore, it has been demonstrated that any period of hyperglycemia may be consequential, leading to macro- and microvascular disease as well as accelerated and exaggerated fetal growth in pregnancy [1]. Excessively low glucose may cause brain damage and lead to death. Oscillating glucose levels, alternating between hyper- and hypoglycemia, may be more consequential, fostering oxidative stress and accelerating apoptosis. In fact, glucose variability or oscillation may prove to be more important in terms of risk of complications than hyperglycemia per se. Consequently, it has become increasingly important to measure and manage the volatility or variability in glucose excursions. Therefore, maintenance of glycemic control within a very narrow range becomes paramount in the priorities of diabetes management.

Glucose monitoring has progressed significantly over the last 100 years since Benedict described the analytical methods for measuring urinary glucose [2]. The Benedict assay was the main test for diabetes monitoring for the next 50 years until the glucose-oxidase reactions were discovered in the 1950s and later was used to measure plasma glucose, initially manually and afterwards by automated methods [2]. Further advances involved the development of glucose strips, self-monitoring of blood glucose in the 1970s, and the emergence of continuous glucose monitoring in 1999 [2]. The development of CGM was a real revolution in diabetes care because it provided the whole daily picture of blood glucose values [3]. The first needle-type continuous glucose sensor was developed by Shichiri et al. in 1982, and CGM devices based on glucose-oxidase were proposed starting from 1999, when the US Food and Drug Administration (FDA) approved the first professional "minimal needle" CGM system to be used by health care professionals, to enable the possibility of analyzing prospective data for review [4]. The first system had several limitations, including inaccuracy, which was confirmed by comparing CGM results with measurement standards [4]. Revolutionary advances in CGM technology included improved accuracy, use of smaller and less invasive devices, extended sensor life, approval for insulin dose decisions, and elimination of finger sticks, reducing the burden for patients [2]. These improvements have resulted in advances in the integration of continuous insulin infusion (insulin pumps) and automated insulin delivery (closed loop systems), along with the need to create newer CGM metrics beyond self-monitoring of blood glucose and HbA1c measurement [2]. Among these metrics, the mean absolute relative difference (MARD) is the most common metric used to assess CGM accuracy [4]. CGM comprises a sensor that measures interstitial glucose levels, a receiver or monitor that displays data and a transmitter that enables communication between the sensor and the receiver [3].

Rationale and Comparison with Other Methods of Glucose Monitoring Hemoglobin A1c (HbA1c) is the result of a nonenzymatic process that represents the percentage of circulating hemoglobin that is glycated and is used as an index of average blood glucose over 3 months [5]. It is a benchmark of blood glucose monitoring, easy to obtain and predicts the risk of microvascular and macrovascular complications [5]. HbA1c has a number of advantages: (1) lower biological variability as compared with fasting or 2-hr

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glucose measurement; (2) it is an index of glycemic exposure by comparison with glucose levels, providing a window into past hyperglycemia over the prior 2–3 months; (3) it does not need to be measured in the fasting state; (4) it has fewer preanalytical factors that may affect the results; and (5) it has become increasingly familiar to patients and health providers [6]. However, HbA1 only provides an approximate measure of glucose control and is not helpful to assess glycemic variability or hypoglycemic events [5]. CGM is a helpful tool to overcome the limitations of HbA1c [5]. Time spent in range and time spent in hypoglycemia are the main CGM metrics that allow for personalized diabetes management [5]. CGM systems measure glucose levels in the interstitial fluid [2–4]. For a period of 10–14 days CGM provide reliable estimates of glucose metrics for 3-month periods, and as a result, it may be useful to estimate HbA1c levels for that period if 70% of the CGM data are available [5]. CGM is the best example of precision medicine in diabetes, albeit interstitial glucose readings have a 15-minute time lag and CGM results do not always match finger stick blood glucose readings [5]. HbA1c is invaluable for diagnosis and management of diabetes, but it does not provide information on hypoglycemic episodes or glucose variability. CGM provides detailed information on glucose patterns, it can detect hypoglycemia and short-term glucose variability and has highlighted limitations of HbA1c testing [6, 7].

With the advent of CGM, it has become feasible to visualize and potentially manage the diurnal glucose patterns of people with diabetes without confining them to hospitalization in order to detect overnight dysglycemia. It is also possible to characterize diurnal glucose perturbations and to detect the slightest abnormalities in glucose metabolism under conditions of daily living thereby improving the potential to ameliorate them. However, before continuous glucose monitoring could be translated into clinical use, it was subjected to intense scrutiny due to its mechanism of measurement. There are currently two types of CGM system technologies: real-time CGM (rtCGM) and intermittently scanned CGM (isCGM), which is often referred as "flash CGM [2]. rtCGM uses a sensor 5 mm in length placed under the skin in the interstitial fluid. Coated with glucose oxidase, it measures glucose in the interstitial fluid by converting the chemical reaction into electoral current. This "current" is stored in the sensor/transmitter and "sent" (transmitted) wirelessly as an electrical signal to a special receiver. Since the signal between the transmitter and receiver is constant, the receiver must be kept in close proximity, usually within 3 feet of the transmitter. The continuous signal is sent in 1, 5, or 10-minute intervals, dependent upon manufacturer. Also manufacturer dependent are the length of time the sensor remains in place—currently up to 7 days. Finally, the receiver can be uploaded to a computer where proprietary software produces a variety of reports.

Because the sensor is placed in the interstitial space, its measurement of glucose differs from a simultaneous measurement of glucose in blood, such as reported by SMBG capillary testing. Interstitial glucose is the result of glucose in the bloodstream being transferred into the interstitial fluid (or tissue fluid) via passive diffusion. The interstitial fluid bathes and surrounds all cells. When the volume of glucose in the blood stream (capillary system) is greater than in the interstitial fluid (ISF), the glucose migrates into the ISF. From the interstitial fluid, the glucose moves into the target cells (in insulin sensitive tissue with the assistance of insulin). Thus, there is a difference between glucose levels found in the blood and the ISF due to the lag time for the passive diffusion. The difference can be conceptualized as time sensitive. If glucose in the blood moved quickly into the ISF, the lag would be an insignificant factor. However, the time lag ranges for from 5 to 15 minutes. The difference can be significant if real-time glucose levels were guiding clinical decisions, especially under conditions of rapid change in blood glucose. To mitigate this, CGM device manufacturers use calibration to blood glucose [8]. The patient uses SMBG to obtain the current reading and enters this value into the CGM receiver. The receiver uses a proprietary algorithm to readjust the current CGM reading; consequently, the greater the number of calibrations the more accurate the CGM reading when compared to SMBG. Thus, current CGM devices require up to four calibrations each day.

The algorithm needs to take into account the time lag and value differences. Because the time lag may be a problem for patients dependent upon real-time blood glucose levels to control insulin administration either by pump to multiple daily injections and because CGM devices sound alarms when glucose levels reach low thresholds, accuracy has become a major issue with regards to routine use of CGM for clinical decisions. Additionally, because calibration values are entered manually and rely on patient skills to obtain the sample and enter the correct value, utilization of CGM for real-time diabetes management has become problematic.

In 2014, a new form of CGM was introduced. Called flash glucose monitoring (FGM), it uses the same chemical glucose oxidase mechanism for glucose measurement as CGM with updated wired enzyme sensors incorporating osmium [9]. Because this sensor technology does not produce as much "drift" as earlier sensors and has a more stable response over time in glucose measurements, it can be calibrated at the time of manufacturing and does not require recalibration by the patient. A second innovation is that the new technology allows the sensor to stay in place for 14 days.

How does the factory-calibrated system compare to a patient-calibrated version? When patients simultaneously wore the FGM system with factory calibration and with patient calibration, the difference in glucose values were negligible, but favoring the factory-calibrated system [4]. Thus, these innovations, when tested against standard CGM (with calibrations by the patient), are more closely correlated to blood glucose measured simultaneously. This is possible because the sensors are calibrated against blood samples in the manufacturing process; consequently, each batch that is produced has the same adjustment to blood glucose. It has been reported that each patient's blood glucose level and interstitial glucose level was different and required ongoing frequent calibrations (essentially SMBG values) to correct for these difference. However, there is an intrinsic problem with SMBG-based calibrations that CGM manufacturers overlooked. They made the assumption that patients would accurately, frequently, and correctly calibrate their CGM devices using SMBG meters that were constantly being reassessed for their own accuracy. In practice, however, it was possible that patients skipped SMBG, inaccurately entered calibration values, and used outdated or error-prone SMBG meters. In short, the patient calibrations were subject to more error and greater variability than factory-calibrated sensors. In additional, the wired enzyme technology was made for a more stable and consistent measurement, thus reducing the likelihood of sensor-to-sensor variability.

Another significant difference between standard CGM and FGM is how the information (glucose values) is stored, transmitted, and reported. CGM sensors constantly measured glucose and passed electrical signals to the transmitter, which converted the electrical current to a format that could be continuously transmitted to a nearby receiver. The receiver stored the data in a manner that could be uploaded to a computer which, using proprietary software, aggregated the data into a series of reports. Due to the proprietary nature of the software, the reports were not comparable among manufacturers. Some companies accumulated the data in 5-minute intervals while others used 10-minute intervals. Thus, based on the manufacturer, the graphic displays could have as many as 288 points to produce a 1-day curve.

FGM uses a novel approach to capturing, storing, and reporting glucose data. To understand this best, it is important to know that unlike CGM devices, the FGM receiver (reader) functions to capture sensor data only when the user passes the reader over the sensor, such as when the patient wants to determine how much insulin to take or how a particular meal affected the postprandial glucose level.

Both CGM and the newer FGM are advances on SMBG. Throughout the world, patients are asked to measure glucose by SMBG anywhere from once to multiple times each day. Based on these readings, clinical decisions related to medication adjustments are made by the patient and often by the doctor as well. Taken in isolation, these values are often given great clinical value. For example, a single fasting glucose may be used to titrate insulin, determine overnight glucose values, and provide an overall assessment of glycemic control. Similarly, one or two postprandial hyperglycemic value, taken 1 hr after the meal, may lead to a change in diet or medication dose (especially insulin) as would a single hypoglycemic value, which often causes a cascade of events resulting in alterations in medications. Because in most clinical practices patients are seen infrequently, three to four times a year, SMBG values take on even more significance. As based on these data as well as HbA_{1c}, the decision at the clinic may be used to determine the next several months' regimen.

Figure 30.1 depicts this clinical dilemma of using SMBG data to make decisions. Looking at just the SMBG data, a clinician would assume normal fasting and midday postprandial values with evening hyperglycemia. The SMBG provides no indication of overnight hypoglycemia. The

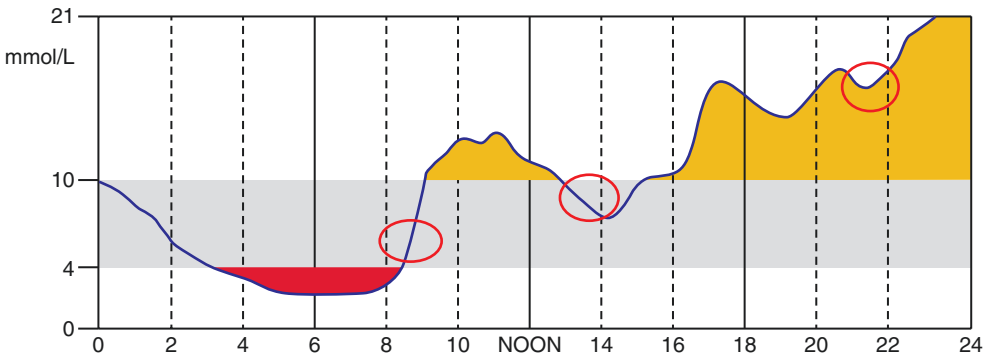

Fig. 30.1 One day of continuous monitoring with circles representing periods of SMBG data. If only the SMBG data are used, then the interpretation would suggest normal fasting glucose (7 mmol/L at 9:00), normal post mid-day meal glucose (10 mmol/L at 13:00), and significant hyperglycemia in the evening. If the continuous graph were used, it would show overnight hypoglycemia, post breakfast hyperglycemia, and midafternoon to midnight hyperglycemia

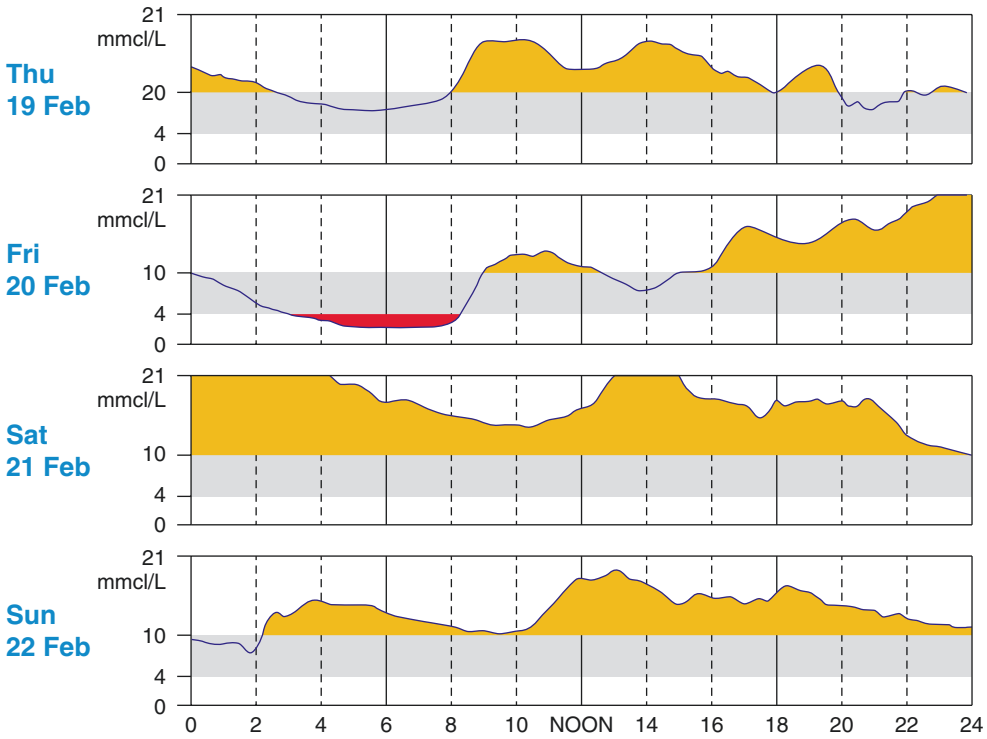

Fig. 30.2 A sequence of four days of CGM. In this sequence, while on the first day, glucose levels tend to be above the target (gray zone), then on the next day there is overnight hypoglycemia, while on the subsequent two days there is almost continuous hyperglycemia

consequences for clinical decision-making can be significant. Clearly, the complete diurnal pattern leads to a different interpretation than a single or even multiple SMBG tests. The CGM curve clearly shows that between 4 and 8 AM glucose dips below 4 mmol/L. Additionally noted in the CGM curve is the degree of instability in glucose level with more than 18 mmol/L difference between nadir and apex.

Figure 30.2 is a sequence of four consecutive days using continuous data. The first day's pattern gives no indication of impending overnight hypoglycemia, while the second day's pattern does not suggest the next 2 days of significant hyperglycemia. The first day does not appear to predict the second day, or the last 2 days in the sequence. The intraday variability is significant, since it suggests that any clinical decision based on these 4 days may be misleading.

Ambulatory Glucose Profile (AGP): an innovative approach to clinical decision-making using continuous glucose data.

Clearly, as shown in Fig. 30.2, each individual day does not appear to produce an underlying metabolic pattern that characterizes the next day. The curves appear to be unstable, reversing direction several times each day. These changes in direction appear volatile on some days and at other times smooth. This volatility from nadir (between 4:00 and 8:00 to apex (at midnight) has been associated with *oxidative stress and consequential apoptosis*. Can a clinical decision be made in the face of such volatility? Is there a discernable pattern? The ambulatory glucose profile (AGP) employs the individual glucose values that are collected via CGM and depicts these values as five continuous frequency curves as shown in the top panel of Fig. 30.3 with the 14 days (midday on the first and last days) that comprise the AGP data in the bottom panel.

Looking at the daily graphs, there does not appear to be a clear pattern. However, when the daily graphs are superimposed on one another, a pattern (AGP) emerges. Note that the range of glucose values does not differ throughout the modal day. Also note that the values do not appear to be following a normal distribution about the median (center curve). By plotting the mean the diurnal, glucose pattern would be misrepresented. It would suggest that glucose is normally distributed and that the mean and standard deviation represent both the central tendency and the dispersion of glucose values over multiple days. Instead, the median is plotted and the glucose ranges are represented as frequency distributions. In this example, hypoglycemia occurs infrequently, between 20:00 and 24:00 hrs on February 19th. This is depicted on the AGP by the inter-decile range curve as dipping into the hypoglycemic range in the diurnal pattern between 20:00 and 24:00 hrs. This would suggest that the risk of hypoglycemia is less than 10% between those hours.

Shown on Fig. 30.4 is the same AGP in Fig. 30.3 with each of the five frequency curves labeled. As illustrated in the AGP, the five curves depict the glucose dispersion. From top to bottom they are: 90th percentile, 75th percentile, 50th percentile (median), 25th percentile, and 10th percentile. The area between the 25th and 75th percentile is known as

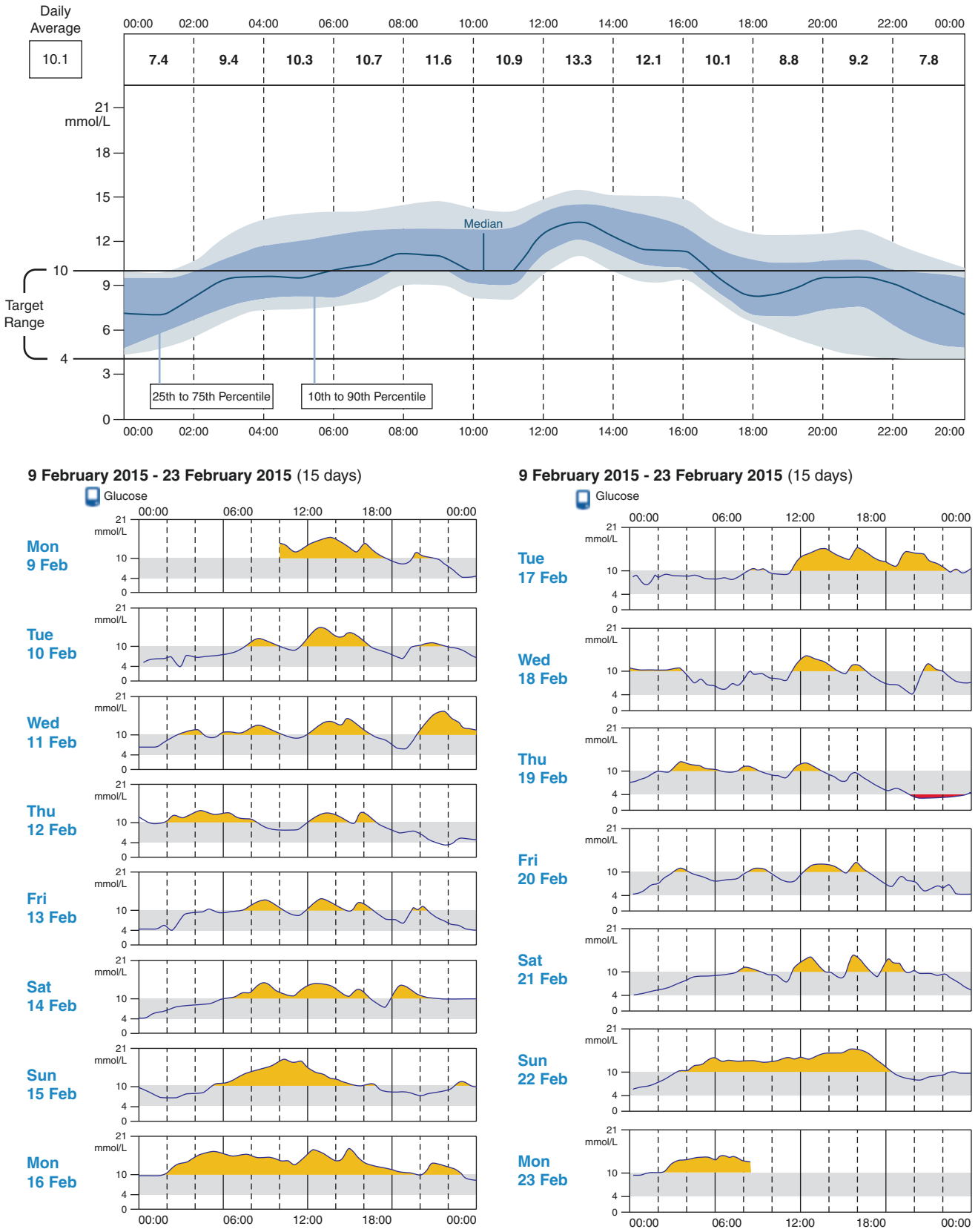

Fig. 30.3 AGP and the 14 days it represents. The top panel is an AGP which is comprised of the 14 days of data collected using CGM. The AGP disregards the dates and plots all values according to time of day. The AGP reflects the overall glucose exposure, variability, and stability for the time period. The light gray zone represents the inter-decile range, the dark gray the inter-quartile range, and the dark single center cure represents the median. The underlying pattern shows a rise in glucose throughout the day time hours with a descent beginning at 2 PM and continuing into the evening. Overnight glucose appears to rise beginning at midnight

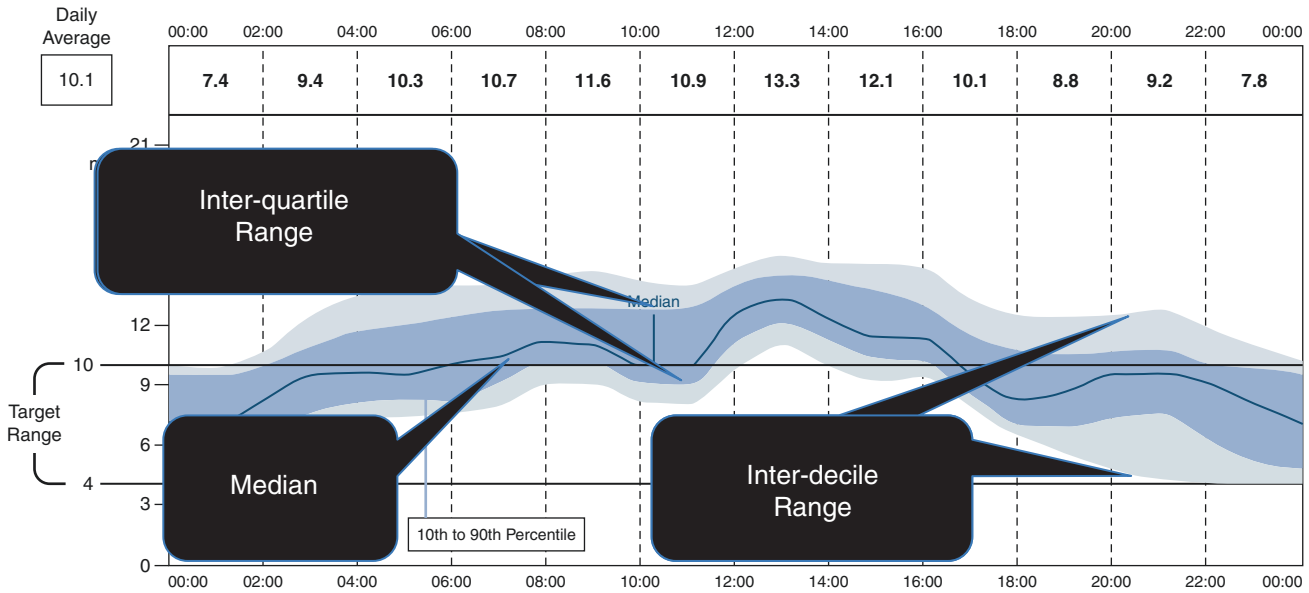

Fig. 30.4 An AGP showing its key components. The AGP comprised of five frequency distribution curves marked here by the callouts depict the glucose exposure and variability over the 14 days represented in this diurnal pattern

the interquartile range (IQR). Fifty percent of all values at each time period fall within this range. As shown in Fig. 30.4, at midday the interquartile range is 3 mmol/L (the difference between 9 and 12 mmol/L) while at midnight the IQR widens to 4 mmol/L. While the IQR is one measure of *glucose variability*, a second measure, the inter-decile range (IDR) represents the difference between the 10th and 90th percentile curves. Eighty percent of all values fall between these curves. As both the IQR and IDR narrow the certainty of where the values will fall improves. In Fig. 30.4, between midday and 16:00 hrs, the glucose ranges (or variability) are narrowest, while between 20:00 and 24:00 hrs they are widest. The five curves that comprise the AGP "force" the eye to see the overall pattern lessening the interpretive significance of outlier values. The curves provide insight into the daily perturbations in glucose metabolism that characterizes diabetes.

In order to assure clinical significance, the AGP must characterize more than glucose variability. Glucose exposure and stability are additional important characteristics of overall glycemia control. Glucose exposure is measured by the area under the time curve (AUC) and is time dependent. The question that needs to be answered is, "How much glucose is the individual exposed to over a typical or modal 24 hour period?" More specifically, "how much *excess* glucose exposure is the individual subjected to, as that constitutes the injurious exposure?" In contrast, glucose stability is a relatively new concept related to the degree of change from moment-to-moment the individual with diabetes is experiencing. Together, these two characteristics aid in the interpretation of the diurnal glucose pattern.

Shown in Fig. 30.5 are two daily profiles for which the area under the curve is measured (using a "modified" trapezoidal method) by segmenting the daily profile into 24 hourly segments. Between 6:00 and 7:00 area, under the top panel is 6 mmol/L/hr. versus 10 mmol/L/hr. for the next day shown in the lower panel. This is repeated for each hour of each day. In terms of the 14 days that comprise the standard AGP, the best representation of these data is the median of the AGP for the time period under examination. Thus, *glucose exposure* is measured by segmenting the AGP median curve into 24 equal parts each representing 1 hr (along the *x*-axis) and the height of the curve (hourly median) as the *y*-axis glucose level. Area under the curve (Fig. 30.6) is therefore: $\text{AUC} = \sum_{i=0}^{24} P_{50_i}$ where i = hr of the day and P_{50i} = the smoothed 50th percentile value for the ith hour of the day. The value is displayed as mmol/L*24 hr.

Normalization of AUC is calculated by dividing the total by the number of hours for the time period (e.g., for a 24-hr period, the total would be divided by 24). To measure glucose exposure over a specific time period, the area under that part of the curve is measured. In this example. The overall exposure is 244 mmol/L*24 hr. Normalized it would be 10.2 mmol/L/hr.

To measure excess glucose exposure the criteria is set to the median target (6 mmol/L), the targeted 24-hr exposure would, therefore, be: 144 mmol/L*24 hrs. The excess exposure is, therefore, 100 mmol/L*24 hrs (normalized to 4.2 mmol/L/hr).

Since the visual evidence shows that a single day does not appear to predict the same diurnal pattern on subse-

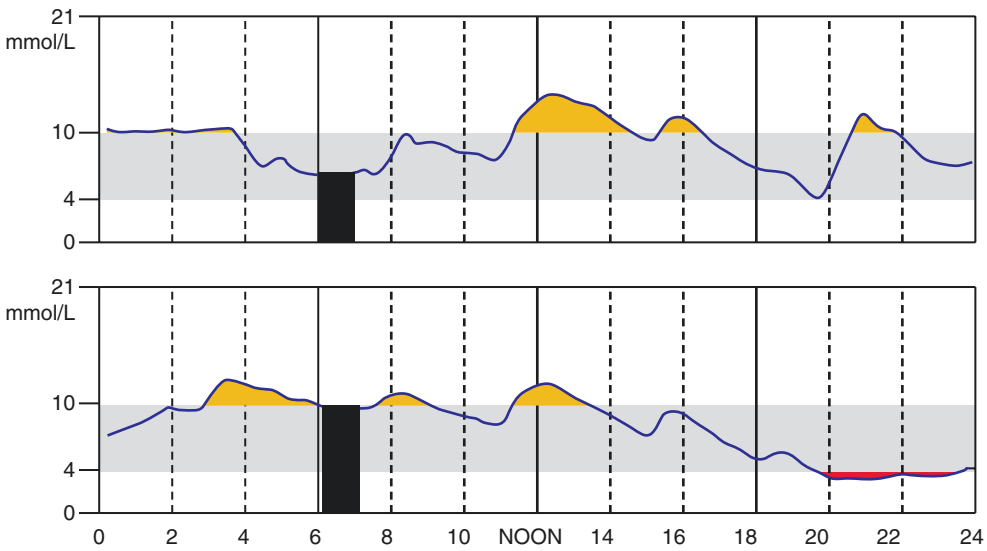

Fig. 30.5 Daily profiles showing the area under the curve between 6:00 and 7:00. The two rectangles represent the area under the curve between the time periods. Measured as height in glucose and time in hours

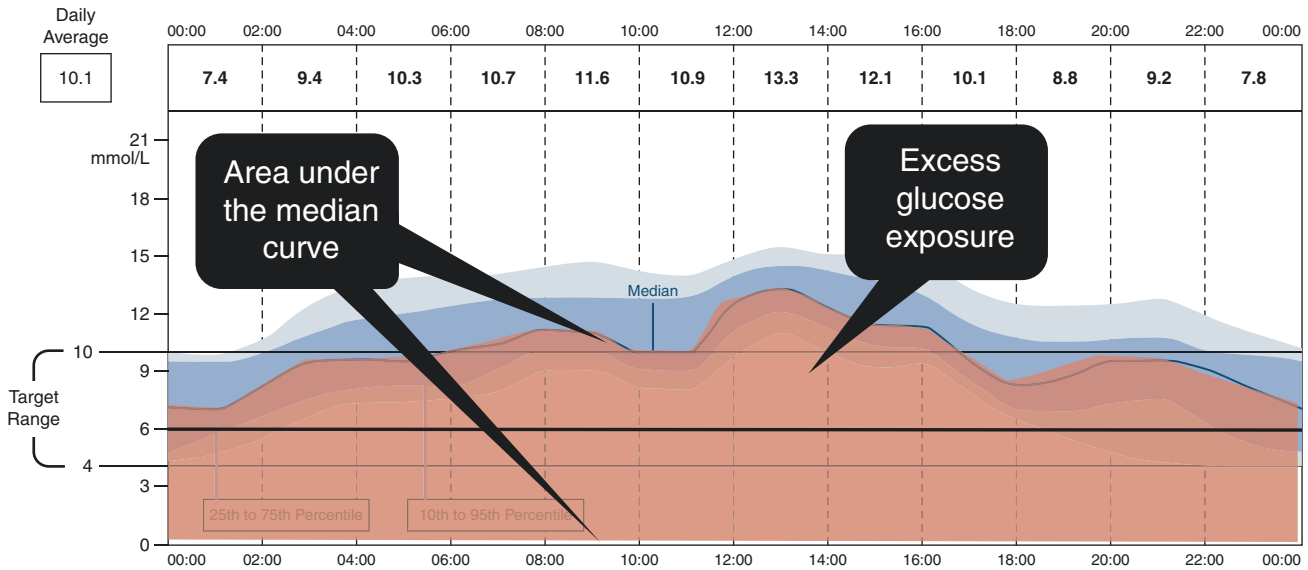

Fig. 30.6 Glucose exposure as measured by the AUC and excess exposure. Glucose exposure is shown as the darkened area under the median curve. The excess area is shown as the area above 6 mmol/L

quent days, what number of days would be required? A major multicenter trial studying this question in 185 subjects with type 1 and type 2 diabetes showed that 14 days of CGM data predicts the pattern for the next 90 days assuming there is no substantial change in treatment [10]. They found that for 3 days of sampling, the r [11] value ranged from 0.32 to 0.47 when considering "…mean glucose, percentage of values 71–180 mg/dL, percentage of values >180 mg/dL, percentage of values ≤70 mg/dL, and coefficient of variation; in contrast, for 13–15 days of sampling, the r^2 values ranged from 0.66 to 0.75. The results were similar when the analysis intervals were stratified by age group (8–14, 15–24, and ≥25 years), by baseline hemoglobin A_{1c} level (<7.0% vs. ≥7.0%), and by CGM device type." Based on these data, they concluded that "a 12–15 day period of monitoring every 3 months may be needed to optimally assess overall glucose control." Thus, it appears that the minimum amount of days of monitoring to predict exposure, variability, and stability for up to the subsequent 90 days is 14 days.

Our own studies have shown that AUC is statistically equivalent to the average of the total daily glucose exposure of the 14 days and thus is the "best fit" representative of the overall glucose exposure that characterizes the period under investigation [3]. Similarly, any time period under the median is a "best" representation of the glucose exposure for that period. To determine the prandial/post-prandial glucose exposure, the hourly medians are summed. To determine

overnight glucose exposure, the sleeping period is noted, and the AUC for that period is calculated.

Glucose stability is a measure of the moment-to-moment change in the glucose level as depicted on the AGP median curve. It is calculated by segmenting the median into hourly periods. Next, the absolute difference between the hourly values is calculated, summed, and divided by 24. The result is the average hourly change in the median. Reported as mmol/L/hr, it provides an indication of the level of stability in glycemic control.

While exposure, variability, and stability characterize overall glycemic control; hypoglycemia and hyperglycemia characterize specific clinical events. The visual examination of an AGP to detect these two dysglycemic states is dependent upon the clinical criteria established by the clinician. In the examples already presented below, 4 mmol/L is generally used to define hypoglycemia and above 10 mmol/L for hyperglycemia. These are arbitrary and in practice individual factors should be taken into consideration such as: age, duration of diabetes, treatment modality, hypoglycemia unawareness, patient goals, and long-term complications. Nevertheless, the AGP allows for quick detection of these two dysglycemic states. In Fig. 30.7 both states are readily discernible. This subject, with an HbA_{1c} of 6.4% spent 48% of his time within target with 26% in hypoglycemic and 26% in hyperglycemia. As can also be seen, the patient's overall control shows significant oscillation in the median curve indicative of poor glucose stability. However, overall exposure was 168 mmol/L*24 hrs or less than 30 mmol/L*24 hrs excess exposure. The questions remains as to whether this profile is sufficient to prevent or reduce the risk of complications.

In 2008, we undertook the first study employing CGM technology with AGP analysis to characterize glycemic control in individuals with normal glucose metabolism [1]. Initially, 62 subjects (32 with normal glucose tolerance and 30 with diabetes) participated employing CGM for 30 days. Prior to the study and following the study, HbA_{1c} was measured as well as insulin levels. HOMA was also completed at initiation to assure that the subjects with normal glucose metabolism had normal insulin resistance. The results (Fig. 30.8), since replicated in more than 250 individuals with normal glucose metabolism who monitored glucose continuously for between 5 and 30 days, give ample evidence that individuals with normal glucose tolerance share several important AGP characteristics: (1) stable glucose levels, (2) minimal variability, and (3) <4% of values within the hypoglycemic range. It has been almost axiomatic that normal glucose levels are 5.6 mmol/L and that they range from 4 to 8 mmol/L; and only under rare metabolic stress are these

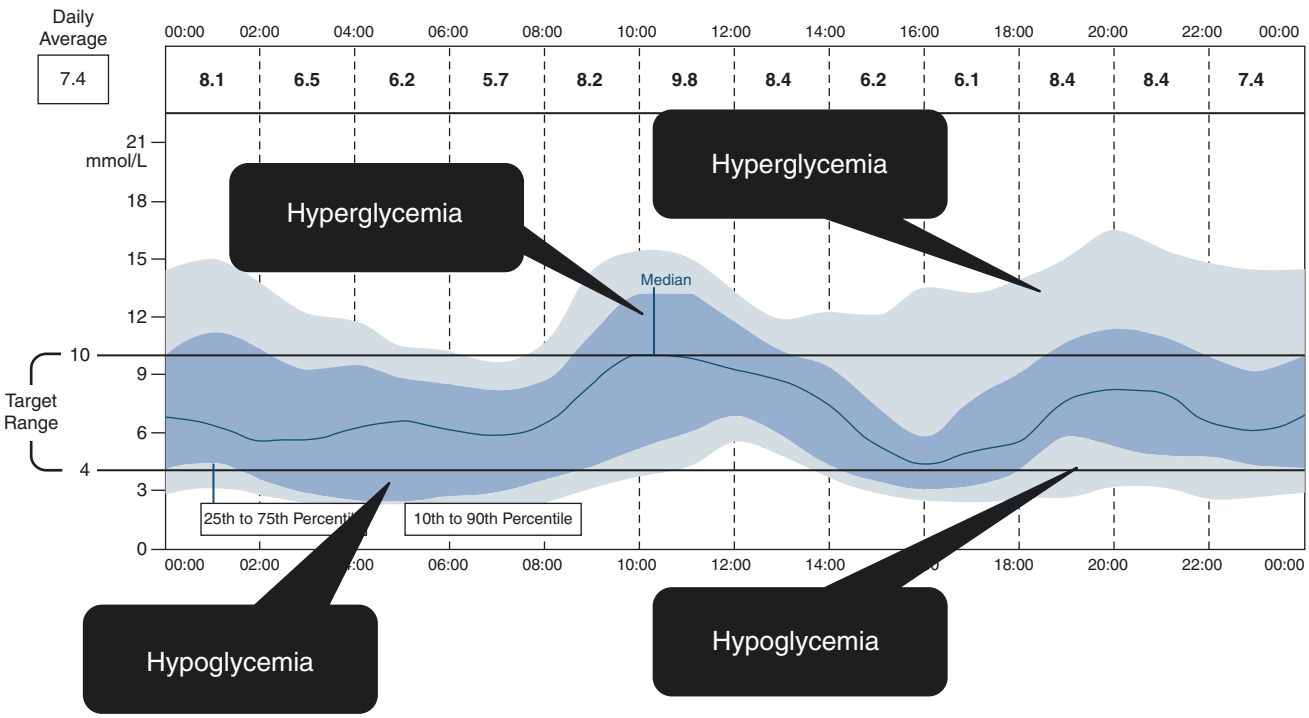

Fig. 30.7 AGP with hypoglycemia and hyperglycemia. The target was set at between 4 and 10 mmol/L. The periods marked with the callouts indicate patterns of dysglycemia. The frequency can be determined by the color of the shaded areas. The first hypoglycemic period denoted by dark shading suggests a risk of between 25 and 50% of the time while the second period suggests less than 25% of the time there will be hypoglycemic episodes. Similarly, the first major period of hyperglycemia between 8:00 and 12:00 has a 50% risk, while after 12:00 the risk drops to less than 25%

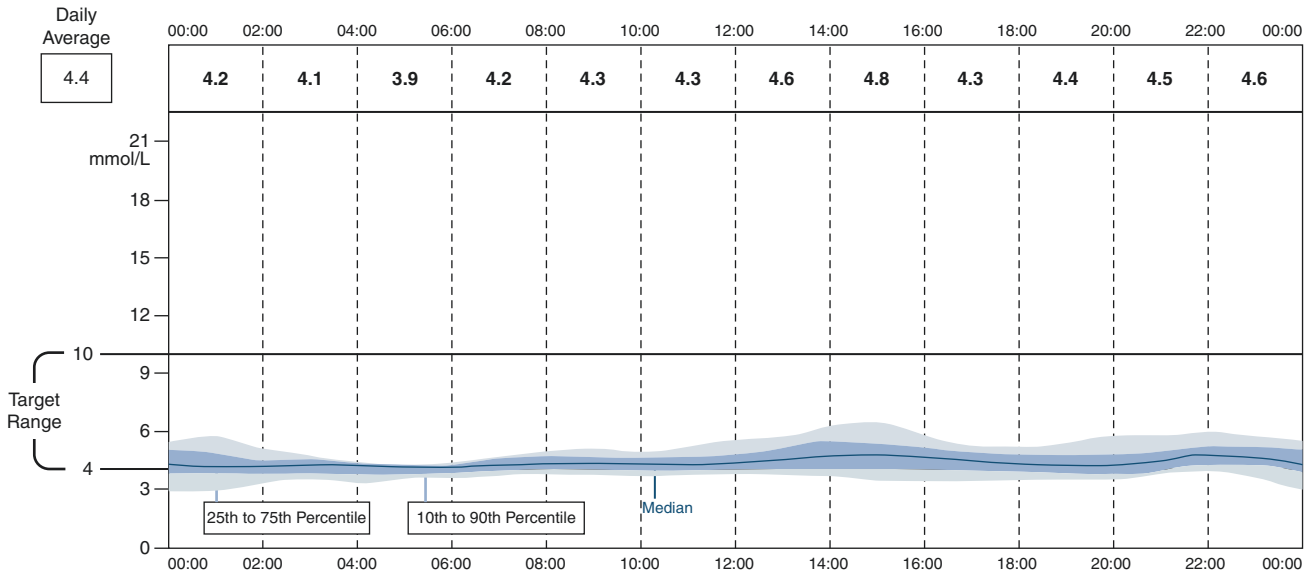

Fig. 30.8 AGP of subject with normal glucose metabolism. This is the typical profile of a person without diabetes. Note that, glucose variability is between 1 and 2 mmol/L, post prandial rises are minimal, and hypoglycemia is present

barriers broken. Interestingly, only since the advent of CGM has it been possible to provide a characteristically "normal" diurnal glucose pattern.

If the AGP of an individual with normal glucose tolerance has such tight parameters, what does this suggest about the goals of diabetes management? Have the treatment goals, which rely heavily on normalization of HbA_{1c}, been misleading? Should emphasis be placed on reduction of glucose variability and improved stability rather than primarily on glucose exposure? If so, how can this be accomplished?

When individuals with normal glucose tolerance are compared to individuals with diabetes among the most salient findings for people without diabetes are: (1) hypoglycemia ranges up to 4% in "normal" subjects; (2) glucose exposure remains within a 27 mmol/L*24 hrs range between the low and the high ends of normal; (3) IQR remains in a narrow range (<2 mmol/L); and (4) change in glucose (glucose stability) hovers at 1–2 mmol/L/hr. which is generally two-thirds more stable than subjects with diabetes.

AGP in Clinical Care

Continuous monitoring should provide a physiologic framework for clinical decision-making in three general areas: (1) detection of the underlying dysglycemia; (2) selection of the most efficacious therapy and guiding adjustments; and (3) measuring treatment effectiveness. How can it be assured that normal glycemia is achieved?

For the AGP to be an effective tool in practice, it must be applied in a systematic manner following the principles of evidence-based medicine. Essentially, it must identify (diagnose) the problem, lead to clinical decisions (find a response), and attest that the response is effective (evaluate clinical outcomes). In this section, flash glucose monitoring (FGM), is used to illustrate how systematic analysis of AGPs provides a rational approach to clinical decision-making. The patient can retrieve glucose levels by passing a receiver over the sensor that is worn on the arm (Libre FGM System, Abbott Diabetes Care, Alameda, CA). The sensor lasts 2 weeks and does not require self-calibration; it stores up to 8 hrs of readings at 15-minute intervals. The receiver stores up to 90 days of data and transmits its results to a PC. The AGP is automatically produced when the data are downloaded to a PC or Mac.

The initial or reference AGP serves to provide an overall depiction of the diurnal glucose pattern and as such has two principal functions: (1) to provide a baseline "measure" against which all future AGPs will be measured and (2) to provide a framework for analysis in which problems can be identified and addressed in systematic manner. Figure 30.9 is the AGP of a person with type 1 diabetes treated by continuing subcutaneous insulin infusion (CSII). It represents the first 2 weeks of wearing the FGM sensor. As a baseline measure, it requires a narrative description. The description addresses four primary characteristics: glucose exposure, variability, stability, and hypoglycemia. As descriptors, it adds a quantitative element (reported through the software or interpolated from the graphics) to each dimension. For example, the overall glucose exposure is 320 mmol/L*24 hrs, which is 152 mmol/L*24 hrs in excess of normal glucose levels. IQR and IDR are 66 mmol/L and 72 mmol/L, respectively. The glucose stability, or change in the median curve, averages at 11.5 mmol/L/hr. This can be seen by visual

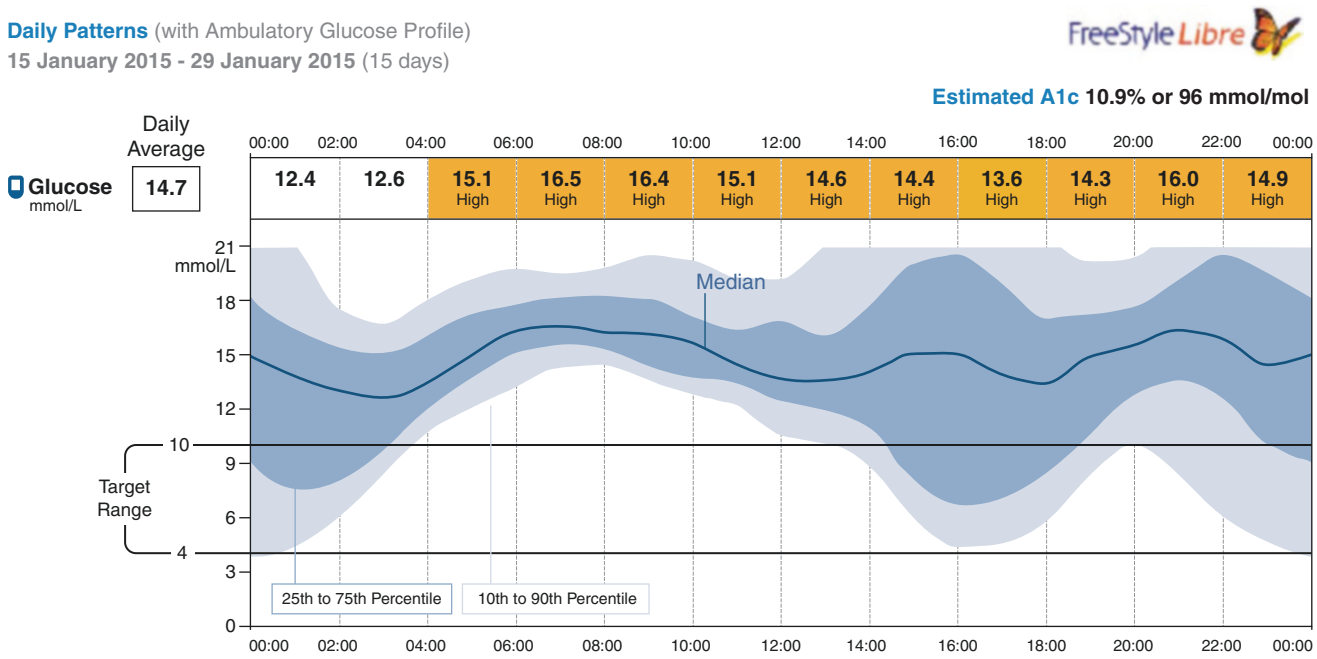

Fig. 30.9 AGP of subject with type 1 diabetes. The boxed number on the top of the AGP are the values of the median reported in two-hour intervals. The shaded boxes indicate that the criteria for "high" was set at 14 mmol/L. The target was set at 4–10 mmol/L. The glucose variability shown as IQR (the dark shaded area) and IDR (the lightly shaded area) ranges from 3 to 18 mmol/L

inspection; the median curve does not experience large swings. There appears to be virtually no hypoglycemia.

As a framework for analysis, the same four components take on a different meaning. They become clues as to the nature of the underlying problems causing the dysglycemia. For this dimension of analysis, it is important to segment the AGP into eight time periods: overnight, fasting, post breakfast, pre-midday meal, post midday meal, pre-evening meal, post evening meal, and bedtime. Some of these periods can be reduced when they overlap. Examining the AGP from this perspective while addressing exposure, variability, stability, and hypoglycemia makes for a comprehensive analysis. For example, while we already know that excess glucose exposure is high, we need to know when this occurs. In this case, it is throughout the day and overnight. Next, where is glucose variability the widest? Examination suggests 0:00–2:00, 14:00–18:00, and 22:00–24:00. Closer examination reveals that the IDC is widest in the evening and overnight. It also appears that glucose stability and hypoglycemia are not problems. The explanation for much of what is seen lies with the patient. However, before we turn to the patient's information, what conclusions can already be drawn? Without examining the HbA_{1c}, it is already apparent that the patient experiences significant and persistent hyperglycemia, suggesting that insufficient insulin is being delivered. Examining the variability suggests that the glucose levels throughout the night and late in the day is unpredictable from day to day (examining daily profiles would corroborate this). From waking to midafternoon while the glucose is high it remains stable and experiences narrow variability. This suggests a more predictable set of behaviors in terms of insulin administration, diet, and exercise. In contrast, the rest of the day and overnight the patient seems to alter behavior and insulin dose leading to wide variability. A discussion with the patient confirmed that the patient changed meal content and insulin dosing most in the late afternoon and evening as meal timing and content was unpredictable. In contrast, the patient had the same breakfast each day and did not need to adjust the basal or bolus insulin settings.

The multiple issues found in the first AGP can be addressed systematically. First and foremost, is the patient in any imminent danger, especially from hypoglycemia? In this case, the answer appears to be a resounding no. However, if one examines the three periods when the IDR dips into the near hypoglycemic range it suggests that adding insulin throughout the day and overnight is not the initial solution. Therefore, the variability needs to be reduced first; after which, the excess glucose exposure can be addressed. How is this accomplished? Since variability is primarily influenced by insulin administration and diet, these two variables must be attended to first. Limiting the number of basal and bolus settings, fixing the dietary intake to be more consistent, and educating the patient concerning carbohydrate/insulin ratios are methods of stabilizing behavior.

In the sequence of AGPs shown in Fig. 30.10, the effect of a systematic analysis followed by targeted interventions is shown. The first step was to reduce the variability by stabilizing the diet and reducing the need to adjust insulin infusion

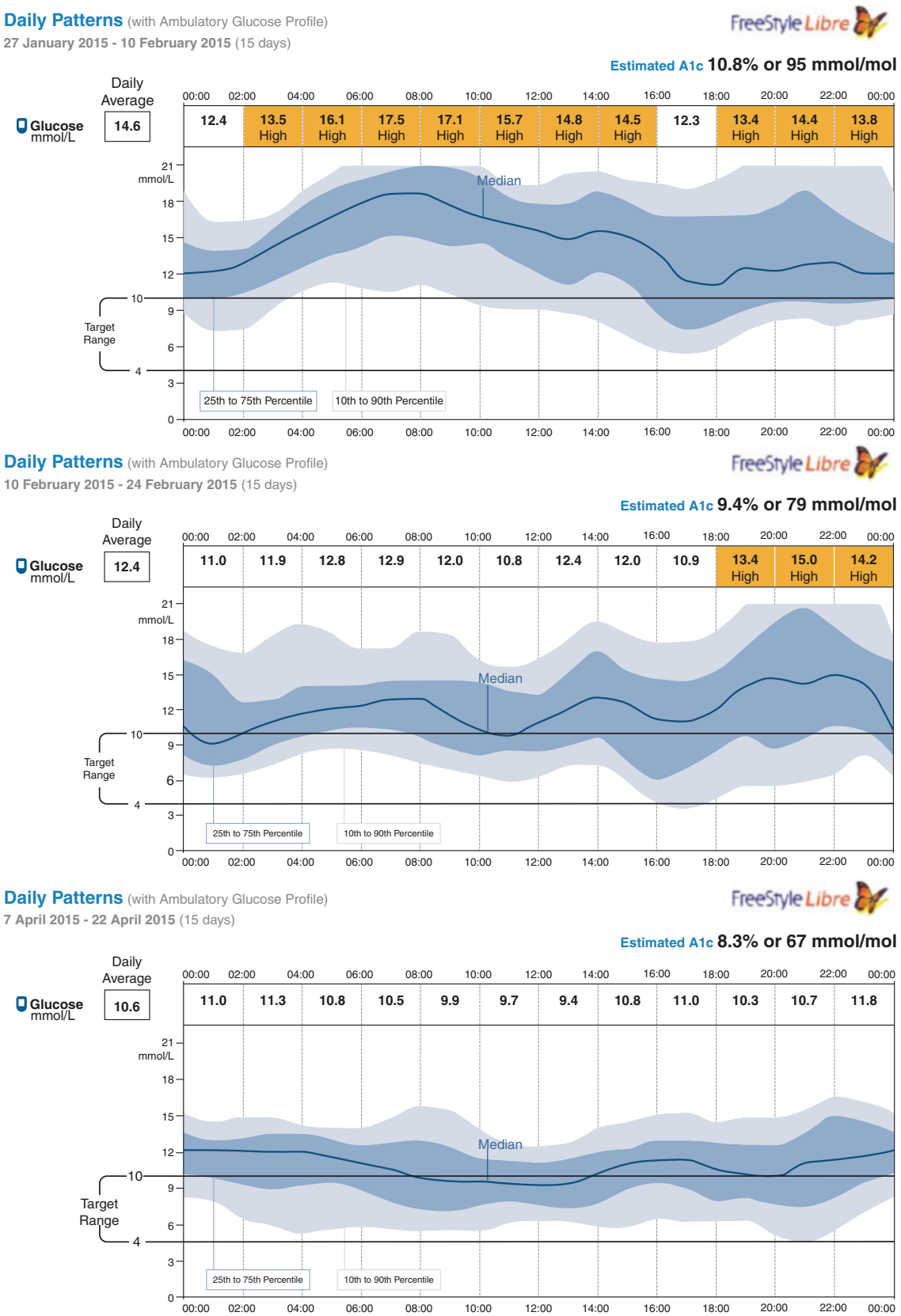

Fig. 30.10 Sequence of AGPs following intervention. The three AGPs are dated showing the impact of treatment over a four-month period. Note on top of each AGP is the median glucose level for each two-hour interval. In the first ten of 12 values were in the high range. In the final AGP none of the values reached this range. Glucose variability also reduced as did overall glucose exposure. Note that glucose stability was unaffected and there was no increased risk of hypoglycemia. HbA_{1c} reduced by 2.5 percentage points paralleling reduction in mean and median glucose levels

rates by improving the calculation of the insulin/carbohydrate ratio. Note that the variability is narrowed, but the HbA_{1c} remained unchanged. The second step was to increase the basal insulin while further improving the insulin/carbohydrate ratio. The final step, once the variability was addressed, was to increase the basal insulin and further adjust the bolus insulin. Note the improvement in the final AGP produced 4 months after the initial FGM.

Conclusion

The advent of continuous glucose monitoring nearly 20 years ago and its continued improvement have led to more efficient and long-lasting sensors reducing a major obstacle to CGM use. There is a strong evidence for CGM use in people with type 1 diabetes, and while the evidence for its use in type 2 diabetes is less robust, similar benefits have been demonstrated [12]. CGM has limitations including cost, accuracy, and perceived inconvenience, but cost effectiveness analysis have indicated that CGM is a cost-effective adjunct to type 1 and type 2 diabetes management and that its use is likely to increase as efficacy data accumulate further and its costs gradually decrease [12, 13]. In the era of COVID-19, the importance of remote glucose monitoring is highlighted now more than ever [14]. Despite these advances, there is one more obstacle to overcome. The translation of this technology into practice requires a standardization of the manner in which the data are reported combined with a systematic approach to their interpretation. Ceriello, in his study of glucose variability and after reviewing AGPs of subject with normal glucose metabolism, wrote, "In people with normal glucose tolerance, blood glucose is maintained in a very narrow range of 3.8–7.7 mmol/L, one can argue that, if the human body spends so much energy to maintain blood glucose levels within such a narrow range, it is because otherwise it would be detrimental [15]." In the series of AGPs included in the article to which he was referring, it was shown that normal glucose tolerance was a balanced state in which various physiological mechanisms worked to prevent oscillations in glucose in order to maintain glucose homeostasis [11]. The article brought forth the notion that without a graphic display of the diurnal glucose pattern, it is not possible to visualize the disruptive nature of dysglycemia. As shown throughout this chapter, when compared to the "normal state," individuals with diabetes experience wide variation in diurnal glucose patterns that without CGM could not be detected.

The AGP provides a standard approach to both a graphic and quantitative representation of CGM and FGM data. It allows for systematic analysis and interpretation. Visualization of dysglycemia, combined with measurement of glucose exposure, variability, stability, and hypoglycemia, presents a basis for standardization. AGP intervention, focusing on reducing the risk of hypoglycemia and hyperglycemia through initial lessening of glucose variability and improvement in stability followed by lowering excess glucose exposure, provides a framework for clinical decision-making.

Management of diabetes often allows a willingness to permit clinical inertia, rather than seek improvement, in part due to the daunting task of finding an effective therapy. While an HbA_{1c} greater than 9% might alarm the practicing clinician, one less than 7% might be reason to be satisfied with treatment in the absence of an AGP. From its inception, CGM with AGP analysis had an underlying purpose, to compel the physician (and patient) to take action. The AGP causes us to examine diurnal patterns suspecting that hidden behind an HbA_{1c} of 7% might be noteworthy hypoglycemia and significant hyperglycemia, as well as considerable variability and instability; all of which are disruptive factors associated with decreased quality of life and increased risk of acute and long-term complications. Finally, a word of caution: after 50 years, SMBG remains equivocal but CGM may face the same fate [16]. For CGM's potential to be fully achieved, it must be understood that it can discover underlying metabolic perturbations that would otherwise go undetected; it can measure the frequency, duration, magnitude, and distribution of glucose variability and stability under conditions of daily living which in turn lead to more precise therapies and improved outcomes [16].

Multiple Choice Questions

1. Individuals with any degree of dysglycemia are at a higher risk of glucose-related macrovascular, microvascular, maternal, and fetal complications when compared to individuals with normal glucose metabolism.
   (a) True
   (b) **False**
2. A feasible method to visualize and potentially manage diurnal glucose patterns of people with diabetes without confining them to hospitalization in order to detect overnight dysglycemia.
   (a) **Continuous glucose monitoring**
   (b) Fasting blood glucose in plasma
   (c) Capillary monitoring of blood glucose
   (d) Post-prandial blood glucose
   (e) None of the above
3. Oscillating glucose levels, alternating between hyper and hypoglycemia are indicative of:
   (a) Ineffectiveness of drug treatment
   (b) **Oxidative stress and apoptosis**
   (c) The effect of counter-regulatory hormones
   (d) The expected response of people with diabetes

(e) All of the above

4. Continuous glucose monitoring has become feasible:
   (a) To reinforce diabetes management in the hospital
   (b) To visualize and manage glucose patterns at intensive care units
   (c) **To detect the slightest abnormalities of glucose metabolism in daily living**
   (d) To adequately treat hyperglycemic crises
   (e) To reduce the burden of diabetic complications
5. Continuous glucose measurement:
   (a) Uses a 10 cm sensor intravenously placed
   (b) Uses a 1 mm sensor placed on a patch on the skin
   (c) Uses a 5 mm sensor placed in the intra-peritoneal compartment
   (d) **Uses a 5 mm sensor placed under the skin in the interstitial fluid**
   (e) Is noninvasive
6. Flash glucose monitoring (FGM), uses the same chemical glucose oxidase mechanism for glucose measurement as CGM with updated wired enzyme sensors incorporating osmium.
   (a) **True**
   (b) False
7. Simultaneous measurement of glucose in blood is important.
   (a) **Because these readings are helpful to make clinical decisions related to medication adjustments by patients and often by the doctor as well**
   (b) To identify which method is more accurate
   (c) To maintain patients' compliance
   (d) To confirm the ineffectiveness of self-monitoring of glucose
   (e) To detect and treat promptly emergencies
8. When individuals with normal glucose tolerance are compared to individuals with diabetes:
   (a) Hypoglycemia ranges up to 100% in "normal" subjects; glucose exposure remains within a 270 mmol/L*24 hrs range between the low and the high ends of normal; IQR remains in a narrow range (<200 mmol/L), and change in glucose (glucose stability) hovers at 100–200 mmol/L/hr. which is generally two-thirds more stable than subjects with diabetes.
   (b) **Hypoglycemia ranges up to 4% in "normal" subjects; glucose exposure remains within a 27 mmol/L*24 hrs range between the low and the high ends of normal; IQR remains in a narrow range (<2 mmol/L); and, change in glucose (glucose stability) hovers at 1–2 mmol/L/hr. which is generally two-thirds more stable than subjects with diabetes.**
   (c) Hypoglycemia ranges up to 1% in "normal" subjects; glucose exposure remains within a 10 mmol/L*24 hrs range between the low and the high ends of normal; IQR remains in a narrow range (<1 mmol/L); and, change in glucose (glucose stability) hovers at 1–2 mmol/L/hr. which is generally two-thirds more stable than subjects with diabetes.
   (d) Hypoglycemia ranges up to 5% in "normal" subjects; glucose exposure remains within a 28 mmol/L*24 hrs range between the low and the high ends of normal; IQR remains in a narrow range (=200 mmol/L); and, change in glucose (glucose stability) hovers at 1–2 mmol/L/hr. which is generally two-thirds more stable than subjects with diabetes.
9. Continuous monitoring should provide a physiologic framework for clinical decision-making in three general areas:
   (a) Detection of underlying dysglycemia.
   (b) Selecting the most effective therapy.
   (c) Guiding adjustments to treatment.
   (d) Measuring treatment effectiveness.
   (e) **All of the above.**
10. Compared to factory calibrated systems, patient calibration by self-monitoring of blood glucose:
   (a) Is more accurate
   (b) **Is less accurate**
   (c) Is equally accurate
   (d) Is more precise
   (e) Is less precise

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Healthy Lifestyles for the Self-Management of Type 2 Diabetes

31

Karla I. Galaviz and Mohammed K. Ali

Lifestyle Behaviors Among People with Type 2 Diabetes

Unhealthy lifestyle behaviors are among the leading risk factors for disability and mortality globally. In 2019, high fasting plasma glucose, tobacco use, and high body mass index (BMI) were among the main causes of death and disability worldwide [1]. Physical inactivity is also a leading risk factor for the development of noncommunicable diseases [2] and is responsible for substantial economic burdens worldwide [3].

In people living with type 2 diabetes, unhealthy lifestyle behaviors can worsen the disease. Insufficient physical activity, low consumption of vegetables, high salt intake, and smoking are associated with poor glycemic and blood pressure control [4–6], while tobacco smoking is associated with increased risk for vascular diseases and all-cause mortality [7]. Further, individuals who are insufficiently active and follow an unhealthy diet are more likely to have diabetes-related complications than individuals following a healthier lifestyle [8].

Despite this, the prevalence of adequate physical activity, healthy diet, and avoiding smoking is far from what is recommended for people with diabetes. In the United States, 39% of adults with diabetes meet recommended physical activity levels [9], while global data show about 10% of adults with diabetes meet recommendations [10, 11]. Regarding diet, US national data show that the percentage of calories from saturated fat consumed by people with diabetes is above recommendations, while fiber intake is below recommendations [12]. Data from a study of 13 countries show participants with diabetes have poor adherence to diet and exercise self-management programs [13]. Finally, the prevalence of active smoking among people with hypertension or diabetes is 13% in Africa [14] and 25.7% in people with diabetes in the United States [15]. Overall, lifestyle behaviors of people with diabetes are far from meeting recommended levels globally.

Healthy Lifestyle as a Component of Type 2 Diabetes Management

The overarching goal of diabetes management is to expand quality of life (and possibly quantity of years lived) through preventing microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (coronary heart disease, cerebrovascular disease, and peripheral vascular diseases) complications of diabetes. These complications are central drivers of morbidity and result from longstanding or poorly controlled risk factors such as elevated blood pressure, glucose, low-density lipoprotein (LDL) cholesterol, and smoking. Addressing these risk factors is recommended in several diabetes care guidelines: as an example, the American Diabetes Association 2021 Standards of Medical Care recommend people with diabetes should achieve the following treatment goals [16]:

- Hemoglobin A1c (HbA1c) levels of <7.0% (53 mmol/mol).
- Blood pressure of <140 mmHg (systolic) over <90 mmHg (diastolic).
- LDL Cholesterol levels <2.6 mmol/L (<100 mg/dL).
- Do not smoke tobacco.

Achievement of these ABCD treatment goals is low globally. For instance, in the United States, national data show that approximately 63.7% of adults diagnosed with diabetes

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meet the HbA1c target, 65.5% the blood pressure target, 56.6% the LDL cholesterol target, and 80.6% the nonsmoking goal. Only 26.7% meet combined ABC targets, while 21.3% meet ABC targets and do not smoke [17]. A systematic review of Asian low- and middle-income countries found that average HbA1c (6.5–11%), systolic blood pressure (120–152 mm Hg), and LDL cholesterol levels (2.4–3.8 mmol/L) varied greatly and that recommended care goals are not being achieved widely [18]. Data from Central and South America show that the proportion of people with diabetes not meeting targets ranges from 13.0 to 92.2% for HbA1c, 4.6 to 92.0% for blood pressure, and 28.2 to 78.3% for lipids [19].

People living with diabetes can achieve the ABCD treatment goals by following healthy eating and physical activity plans, losing excess weight, avoiding smoking tobacco, or taking appropriate medications. Some people on medication can even achieve and maintain diabetes remission, which has been recently defined as achieving an HbA1c <6.5% measured at least 3 months after cessation of medication [20]. The effects of medication are augmented by lifestyle changes [21, 22], and indeed, patients who diligently adhere to healthy lifestyle behaviors can minimize their need for medications [23].

Following a healthy diet, engaging in regular physical activity, and avoiding tobacco smoking are thus the first-line management recommendations for every person living with diabetes. These lifestyle measures have been shown to improve HbA1c, LDL cholesterol, and blood pressure while also promoting weight loss even when medications are needed to lower these parameters [22]. Evidence from a meta-analysis shows that structured exercise training that consists of aerobic exercise, resistance training, or both was associated with a 0.67% decline in HbA1c levels in people with diabetes [24]. Meta-analytic evidence also shows supervised aerobic or resistance exercise reduce HbA1c by 0.30%, LDL cholesterol by 11.88 mg/dL, and systolic blood pressure by 3.90 mmHg [25]. Breaking sitting time with standing and light-intensity walking have also been found to improve 24-hour glucose levels and improve insulin sensitivity in individuals with diabetes [26].

Regarding dietary modification, a meta-analysis shows dietary changes with or without physical activity modification can lower HbA1c by 0.51% [27]. Another meta-analysis shows that low-carbohydrate, low glycemic index, Mediterranean, and high-protein diets all improve glycemic control by reducing HbA1c from 0.12% to 0.47% [28]. High-fiber diets or supplements containing soluble fiber have also been shown to reduce HbA1c by 0.55% in people with diabetes [29]. Finally, evidence regarding diabetes remission is starting to emerge: the DIRECT diet replacement intervention trial found that 36% of participants receiving a very low-calorie diet achieved diabetes remission at 24 months, compared to 3% of control participants [30]. Table 31.1 summarizes evidence from these meta-analyses.

Table 31.1 Evidence from meta-analyses reporting pooled effect estimates of lifestyle intervention on diabetes treatment goals

Author	Intervention	A1c % point change [95% CI]	Systolic blood pressure mmHg change [95% CI]	LDL cholesterol mmol/L change [95% CI]
Diet				
Ajala 2013 [28]	Mediterranean	−0.47 [−0.64, −0.30]	–	−0.08 [−0.24, 0.08]
	Low-carbohydrate	−0.12 [−0.24, −0.00]	–	−0.03 [−0.12, 0.07]
	Low glycemic index	−0.14 [−0.23, −0.03]	–	−0.07 [−0.16, 0.02]
	High-protein	−0.28 [−0.38, −0.18]	–	−0.16 [−0.41, 0.09]
Silva 2013 [29]	High-fiber	−0.55 [−0.96, −0.13]	–	–
Physical activity/exercise				
Umpierre 2011 [24]	Structured exercise training Aerobic exercise Resistance training	−0.67 [−0.84, −0.49] −0.73 [−1.06, −0.40] −0.57 [−1.14, −0.01]	–	–
Pan 2018 [25]	Aerobic training Resistance training Combined training	−0.30 [−0.60, −0.45] −0.30 [−0.38, −0.15] −0.53 [−0.68, −0.45]	– −5.20 [−9.10, −1.30] -	– – −11.88 [−21.6, −1.08]
Htoo 2016 [31]	Exercise program	−0.56 [−0.95, −0.16]	–	–
Diet and physical activity				
Chen 2015 [32]	Diet, nutritional education and/or physical activity modification	−0.37 [−0.59, −0.14]	−0.16 [−0.29, −0.03]	−0.14 [−0.29, 0.02]
García-Molina 2020 [27]	Diet and/or physical activity modification	−0.51 [−0.67, −0.35] −0.95 [−1.24, −0.66]	–	–
Michaud 2021 [33]	Telementoring for diet and physical activity improvement	−0.30 [−0.31, −0.29]	–	–
Rawal 2020 [34]	Peer- and community member-led diet and physical activity modification	−0.18 [−0.32, −0.04]	–	–
Umpierrez 2011 [24]	Physical activity and dietary advice	−0.58 [−0.74, −0.43]	–	–

Avoiding tobacco smoking is the third lifestyle target of successful diabetes management. Tobacco smoking is harmful in people living with diabetes because it increases insulin resistance and deteriorates glucose control [35]. Individuals with diabetes who smoke have been found to have a higher risk for cardiovascular diseases (CVD), microvascular complications, and premature death than nonsmokers [35]. In contrast, smoking cessation among people newly diagnosed with diabetes is associated with reduced blood pressure [36]. Thus, advising people not to smoke and offering smoking cessation counseling and support to those who smoke are recommended diabetes management strategies [37].

Regarding prevention of diabetes complications, the PREDIMED trial showed participants with diabetes who followed a Mediterranean diet supplemented with extra-virgin olive oil or nuts had a 30% lower incidence of major CVD events [38]. The Look AHEAD study found no difference in CVD events between obese individuals with diabetes receiving a lifestyle modification intervention and control participants [39], but other benefits were accrued from the intervention. These additional benefits include lower disability [40], lower need for blood pressure and lipid-lowering medications [41], and lower kidney disease [42], among other benefits. Overall, these studies suggest CVD risk factors can be reduced through lifestyle modification in people with diabetes; whether this translates to lower CVD incidence may require stricter risk factor control or longer follow-up to become apparent.

Though experimental evidence is insufficient to suggest lifestyle modification lowers mortality risk in people with diabetes, more data are starting to emerge. For instance, observational evidence from a meta-analysis shows individuals with diabetes who follow a healthy lifestyle have 44% lower risk for all-cause death, 51% lower risk for cardiovascular death, 69% lower risk for cancer death, and 48% lower risk for incident cardiovascular disease than individuals with less healthy lifestyles [43]. In the US Diabetes Prevention Program Outcomes Study, which was in adults with prediabetes (i.e., those who have not yet developed diabetes), neither metformin nor lifestyle modification lowered all-cause or cardiovascular disease mortality [44]. The impact of lifestyle modification on mortality in people with diabetes is yet to be determined.

Recognizing this evidence, several diabetes care guidelines have included lifestyle management in their recommendations. For instance, the American Diabetes Association Standards of Care [16], the NICE Diabetes Management Guidelines [45], the Diabetes Canada Clinical Practice Guidelines [46], the Latin American Diabetes Association Consensus Statement [47], and the International Diabetes Federation Global Guideline for Type 2 Diabetes [48] recommend lifestyle modification for managing diabetes. Specific recommendations across guidelines vary but most recommend performing aerobic and resistance physical activity, lowering calorie intake for people with overweight or obesity, avoiding saturated fats, increasing fiber intake, avoiding added sugars, and avoiding tobacco use and excessive alcohol consumption. As an example, here are lifestyle recommendations for adults from the American Diabetes Association Standards of Care 2021 [49]:

Physical Activity

- Most adults with type 2 diabetes should engage in 150 min or more of moderate- to vigorous-intensity aerobic activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity. Shorter durations (minimum 75 min/week) of vigorous-intensity or interval training may be sufficient for younger and more physically fit individuals.
- Adults with type 2 diabetes should engage in two to three sessions/week of resistance exercise on nonconsecutive days.
- All adults, and particularly those with type 2 diabetes, should decrease the amount of time spent in daily sedentary behavior. Prolonged sitting should be interrupted every 30 min for blood glucose benefits.
- Flexibility training and balance training are recommended two to three times/week for older adults with diabetes.

Diet:

- An individualized medical nutrition therapy program as needed to achieve treatment goals, provided by a registered dietitian/nutritionist, preferably one who has comprehensive knowledge and experience in diabetes care, is recommended for all people with type 1 or type 2 diabetes, prediabetes, and gestational diabetes mellitus.
- For all patients with overweight or obesity, lifestyle modification to achieve and maintain a minimum weight loss of 5% is recommended for all patients with diabetes and prediabetes.
- A variety of eating patterns can be considered for the management of type 2 diabetes and to prevent diabetes in individuals with prediabetes.
- Carbohydrate intake should emphasize nutrient-dense carbohydrate sources that are high in fiber and minimally processed. Eating plans should emphasize nonstarchy vegetables, minimal added sugars, fruits, whole grains, and dairy products.

Smoking:
- Advise all patients not to use cigarettes and other tobacco products or e-cigarettes.
- After identification of tobacco or e-cigarette use, include smoking cessation counseling and other forms of treatment as a routine component of diabetes care.
- Address smoking cessation as part of diabetes education programs for those in need.

Barriers to Healthy Lifestyles for Diabetes Self-Management

Adhering to recommended healthy lifestyle behaviors for diabetes self-management is a daunting task. People living with diabetes face daily lifestyle-related decisions, in addition to their everyday responsibilities, and in some cases, medication management and glucose monitoring. This is a 24/7 effort that takes place in diverse settings where barriers at the individual-, interpersonal-, community-, and system-level may arise. These barriers are discussed in this section and summarized in Fig. 31.1.

Individual-Level Barriers

Individuals living with diabetes may face psychosocial and/or socioeconomic barriers that hinder their lifestyle management efforts. Socioeconomic status, which encompasses educational, economic, and occupational status, has been found to impact lifestyle management through whether and how individuals and communities access relevant health-related resources [50]. For instance, a study in Nepal identified the cost of a healthy diet and appropriate footwear as a major barrier to healthy lifestyle behaviors for diabetes self-management [51]. In the United States, minority populations have low utilization of diabetes management support services given the high cost and poor accessibility to such services [52]. Unstable housing and food insecurity also negatively affect lifestyle behaviors and can lead to poor diabetes outcomes [50].

Individuals living with diabetes may also face psychosocial and capability barriers that hinder effective engagement in lifestyle self-management. For instance, a study from India found people with diabetes were unable to follow recommended medication and dietary guidelines due to low health literacy related to diabetes self-management [53]. A study in Nepal also identified lack of knowledge as a major barrier to diabetes self-management [54], while poor under-

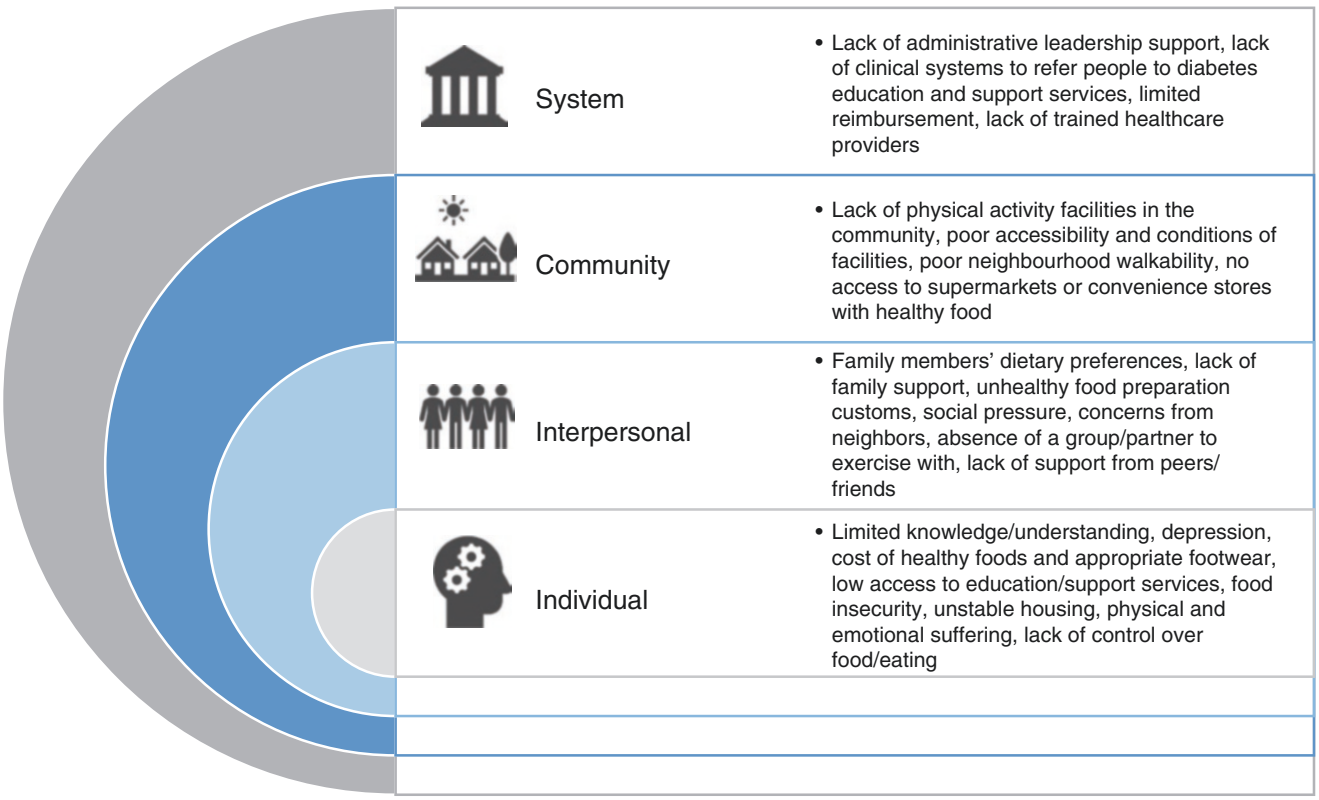

Fig. 31.1 Barriers to effective diabetes lifestyle self-management

standing of diabetes and stress have been identified as barriers to healthy eating in the US [55]. Psychological problems such as depression and diabetes-related distress are prevalent in persons with diabetes and have been found to hinder self-care [13]. Finally, physical and emotional suffering and lack of control over food/eating also hinder lifestyle self-management [56, 57].

Interpersonal-Level Barriers

Family members are the most significant source of social support for a person living with diabetes. Family support promotes diabetes treatment adherence [58] and is associated with fewer psychosocial problems and better self-management among individuals with diabetes [59, 60]. However, families can also negatively impact diabetes self-management. Unhealthy lifestyles of marital partners may increase the risk for cardiovascular disease in the partner dealing with diabetes [61], while family members' dietary preferences can deter healthy eating in those living with diabetes [62]. Further, lack of family support has been identified as a barrier to healthy eating among Hispanics with diabetes in the United States [56] and in Nepal [54]. It is important to also note that family members can also be negatively affected by diabetes as they may experience distress, anxiety and depression, frustration, and lost work/wages due to caring for a relative with diabetes [63, 64].

Friends and groups can also impact lifestyle management through sociocultural influences and modeling. For instance, unhealthy food preparation styles and social events at which food plays a significant cultural role put pressure on people with diabetes to abandon their healthy diet plans [54]. Concerns that neighbors express toward lifestyle management has been found to deter adherence to exercise plans in people with diabetes [54]. Absence of a group to exercise with and difficulty finding exercise partners are prominent barriers to maintenance of exercise routines in people with diabetes [65]. Finally, peers have been found to be both sources of encouragement for physical activity initiation and decreased motivation to be physically active [66]. As such, peers and friends could either act as facilitators of lifestyle management or deter such efforts in people with diabetes.

Community-Level Barriers

For people with diabetes, eating a healthy diet and engaging in regular physical activity may be difficult because healthy foods and physical activity opportunities are not readily available, easily accessible, or affordable in their communities. For instance, lack of recreational facilities in the community or poor accessibility and conditions of facilities can hinder physical activity in adults [67, 68]. In contrast, higher walkability of neighborhoods (e.g., with sidewalks, well-connected, greater mix of land use) has been found to be associated with promising diabetes outcomes [69].

The characteristics of the food environment can also hinder healthy eating in people with diabetes. A study among low-income US adults found people living with diabetes chose poor-quality foods because better-quality foods were out of geographic or financial reach [55]. Similarly, food environments that provide access to healthy foods (e.g., at farmers markets and supermarkets) can facilitate healthy lifestyles in people with diabetes [69]. Low-income and underserved communities are often the most affected with less supportive environmental conditions for physical activity and limited access to stores that sell healthy foods [67, 70].

System-Level Barriers

System-level barriers may hinder the access to, and uptake of, healthy lifestyle support resources. The uptake of the services is suboptimal globally: a study of from 17 countries found only 48% of people with diabetes have participated in educational programs or activities [71], while US data shows 5–7% of individuals who are eligible for diabetes self-management support through an insurance plan actually receive it [72, 73]. System-level barriers that may contribute to this include the lack of administrative leadership support, lack of clinical systems to refer people to diabetes education and support services, and limited reimbursement rates [74]. The cost of such programs is also a barrier in several countries as shown in a review that reports people do not use diabetes self-management support resources due to insufficient health insurance or inability to afford travelling to the program venue [75].

Another system-level barrier that may hinder diabetes self-management is the lack of trained healthcare providers. In the United States, specialized personnel like physical activity counselors, diabetes educators, and dieticians are in short supply [72]. Healthcare providers may also lack training in behavioral therapy and lifestyle counseling, which hinders confidence in their ability to identify psychological problems, lifestyle barriers, or to address these effectively [13]. In South Asia, language and communication discordance between patients and healthcare providers has been identified as a significant barrier to diabetes self-management support [57].

A prominent system-level barrier is the lack of reimbursement policies that support referrals to diabetes education and support in the community. For instance, current reimburse-

ment policies in the United States do not support interventions by nonphysicians or provide disincentives for interventions offered outside the clinical setting [76]. Similarly, Medicare and most health insurance plans in the United States reimburse diabetes education and support services but only if such services align with national standards and mostly when delivered in person [49]. As it is the case for most of the barriers discussed in this chapter, underserved communities are particularly affected by current reimbursement and referral models [77].

Supporting Healthy Lifestyles for Diabetes Self-Management

The barriers previously discussed represent need to be addressed to improve opportunities for people living with diabetes to engage in, and maintain, healthier lifestyles. Innovative ways to support these efforts include offering a variety of diabetes education and support options, using telehealth formats, coaching programs, just-in-time services, online resources, discussion groups, and intense programs for select groups, while leveraging community resources that support healthy behaviors [78]. In this section, we describe different strategies to improve opportunities for engaging in effective lifestyle management. These strategies are summarized in Table 31.2.

Table 31.2 Strategies to facilitate diabetes lifestyle self-management

Individual support	Social support	Community/system support
– Diabetes self-management education and support should be offered to empower individuals with the knowledge, skills, and confidence to engage in lifestyle diabetes self-management. – Education and support can be delivered by specialist nurses, dieticians, lay community health workers, and peer educators. – Education and support should be culturally and age appropriate, tailored to the individual's situation and context, involve family members, and include behavior change strategies. – Education and support can be delivered individually or in group settings, and in person or remotely using trusted telehealth tools (e.g., wearable devices, smartphone applications, and continuous glucose monitors).	– Leverage the support of families and peers to facilitate lifestyle modification. – Provide families with diabetes education opportunities. – Offer behavioral family therapies, training courses, and technologies to support families and build positive relations. – Offer flexible work schedules to help family members miss less days of work. – Identify and train peers to facilitate lifestyle diabetes management and maintain it long-term.	– Foster healthcare–community linkages to connect people with diabetes education and support resources in their community. – Build referral systems to prompt and follow referrals to community resources. – Develop multidisciplinary diabetes care teams that support lifestyle management and ensure referral follow thru. – Adopt/implement healthcare reimbursement models for lifestyle management services. – Healthcare systems should foster coordinated team care, facilitate communication among team members and patients, and connect patients with ongoing support in their communities.

Diabetes Self-Management Education and Support

Diabetes self-management education and support (DSMES) is an effective approach for helping people living with diabetes self-manage their disease. The purpose of DSMES is to empower people with diabetes by giving them the knowledge, skills, and confidence to accept responsibility for their self-management [78]. This responsibility includes collaborating with their healthcare team, making informed decisions, developing personal goals and action plans to achieve them, engaging in problem solving when issues arise, and coping with emotions and life stresses [79].

In the United States, there are national recommendations on effective DSMES to help people living with diabetes navigate their daily self-care. Specifically, the American Diabetes Association recommends healthcare providers offer and modify DSMES at four critical points: (1) at diagnosis, (2) annually or when treatment goals are not met, (3) when complicating factors appear, and (4) when transitions in care or life occur. Regarding lifestyle, these standards recommend that healthcare providers coordinate the full management plan by integrating medical nutrition therapy, DSMES, medications, and physical activity [78].

People with diabetes receiving DSMES have been found to have better clinical, psychosocial, and behavioral outcomes. For instance, a meta-analysis found group-based DSMES was associated with improvements in HbA1c, diabetes knowledge, self-management skills, and self-efficacy [80]. Another meta-analysis showed DSMES can improve quality of life among people with diabetes [81], while a systematic review found DSMES can be used to promote healthy coping [82]. Individual studies have also shown that DSMES is associated with improvements in lifestyle behaviors [83], clinical outcomes [84], and reductions in the presence of diabetes-related distress and depression [85, 86].

In terms of the content and format, education and support delivered by specialist nurses or dieticians seems to have the greatest benefits [87], though evidence also supports the use

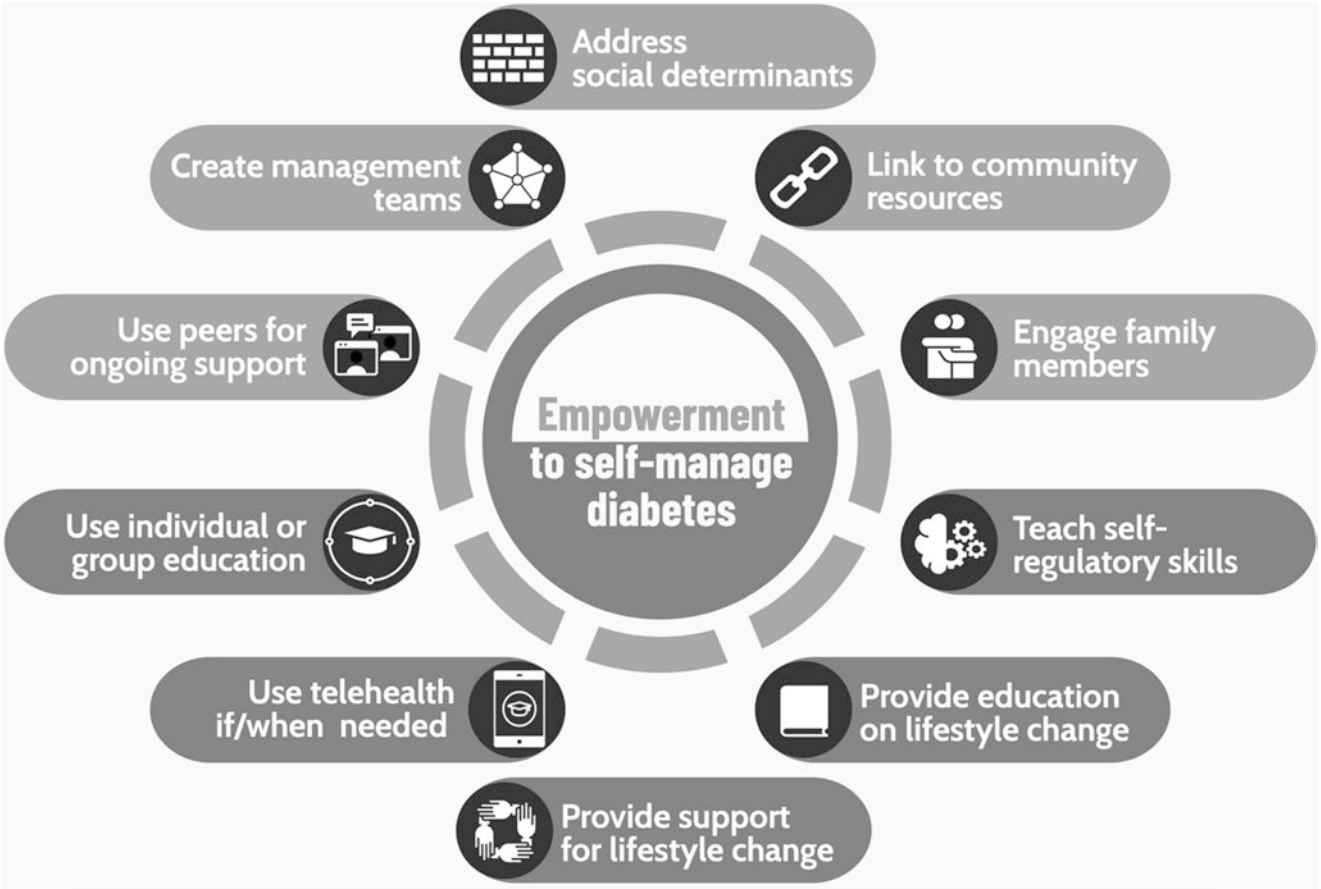

Fig. 31.2 Components for effective diabetes self-management education and support

of lay community health workers [88] and peer educators in providing ongoing support [89]. Education and support programs work best when they are culturally and age appropriate [90], tailored to the individual's situation and context [91], when family members are involved [90], and when behavior change strategies are incorporated [92]. In terms of delivery format, individual and group approaches have similar effects [93], while delivery via telehealth platforms has shown promising results [94–96]. The components of effective diabetes self-management education and support are illustrated in Fig. 31.2.

Social Support

As discussed earlier, family members can be allies or foes in terms of supporting healthy lifestyle choices within the household. Hence, family and household members should be included in, and supported by, diabetes management plans. For instance, families may benefit from psychological support and educational opportunities to improve their capability and motivation to care for their relatives with diabetes. Families should be provided with diabetes education opportunities, such as training courses or educational resources, to learn strategies to support their relatives without affecting their life. Behavioral family therapies, training courses, and technologies can all be employed to support families and build positive relations [97]. Since caring for relatives with diabetes may lead to foregone income by family members, offering flexible work schedules could help family members miss less work days.

Peer support has been found to be an effective component of successful lifestyle diabetes management. Peer support involves the transfer of experiential knowledge about lifestyle behaviors or coping strategies between people who share a particular characteristic [98]. In terms of effective components, peer support models that include lifestyle counseling, goal setting, and behavioral and social support have been found to be effective [89]. Peer support can also help address healthcare access barriers people with diabetes may face, while increasing the quality and quantity of self-management support [99]. Finally, since diabetes requires lifelong care, peer support can be employed to maintain long-term lifestyle management [100].

Evidence on the effectiveness, and the business case especially, for these initiatives may strengthen the likelihood of

employers, insurers, and healthcare systems offering reimbursement or funding for these educational and support services.

Healthcare-Community Linkages

Healthcare-community linkages are needed to connect individuals with resources to implement their lifestyle management activities. Through these links, individuals that are diagnosed/treated in a healthcare setting can be referred to places in their community where they can initiate lifestyle changes and access ongoing support to maintain such changes [101, 102]. To develop successful linkages, available community resources such as education and support programs, peer support groups, exercise facilities, and lifestyle modification programs can be catalogued and included in referral information systems. Identifying trusted resources in the community is also critical given that healthcare providers are unlikely to refer patients if they do not know about quality and accessibility of programs [103]. Healthcare–community linkages are also critical to provide healthcare services that are responsive to social determinants of health [50].

Referrals to community resources can be created through electronic or paper-based systems. For instance, referral strategies can be embedded into electronic medical records with clinical decision support systems to identify patients with diabetes that need referral to a lifestyle management program [104]. Healthcare–community linkages can be further facilitated by embedding and updating resource lists into electronic systems and automating communication technologies to refer patients to relevant community resources; these tools have been shown to improve provider referral rates and patient behavior [105]. Referring people with diabetes may not be enough to achieve effective full engagement in healthy lifestyle modification; therefore, monitoring progress to ensure people follow through and offering ongoing lifestyle support is imperative.

Follow-up and ongoing support can be provided through multidisciplinary diabetes care teams, where part of the team is based in healthcare settings and another part in the community. The role of the diabetes care team is to provide support, provide education, and empower the person with diabetes to take control over his/her/their lifestyle-related decisions [106]. Diabetes care teams may include physicians, nurse practitioners, psychologists, dietitians, exercise counsellors, and diabetes educators, while other models can also include peers [89], community health workers [88], and care coordinators [107]. Healthcare systems that foster coordinated team care, facilitate communication among team members and patients, and allow the provision of ongoing support in community settings would be needed in this endeavor.

Technology and Telehealth

Technology and telehealth approaches can be used to support lifestyle management and facilitate timely healthcare delivery. The evidence supporting the use of these approaches has been augmented by the COVID-19 pandemic, which triggered a large shift toward using these modalities. Still, the evidence specific to diabetes education and support delivery is so far modest.

Evidence from a meta-analysis shows smartphone applications can be used for reminding, monitoring, and coaching people with diabetes to improve their lifestyle behaviors [95]. Similarly, an integrative review concluded that web-based learning and mobile health applications can improve diabetes self-management behaviors [94], while Internet-based interventions that employ behavior change techniques (e.g., goal setting, action planning) and offer peer support can improve lifestyle behaviors [102, 108]. In 2021, a meta-analysis identified telemonitoring with automatic mobile transmission and real-time feedback for supporting lifestyle changes as a promising option to enhance diabetes management [33].

Telehealth has the potential to address accessibility barriers some individuals may face. Internet-based strategies and smartphone applications have been used to reach patients that do not have access to traditional healthcare services and to link them with relevant providers [94]. In situations where access to the Internet or cellular data are limited or not available, telephone calls or text messages from healthcare providers could be employed, which have been shown to promote effective self-management [109]. However, telehealth models should address the digital barriers found in rural populations, older adults, racial/ethnic minority populations, and those with low socioeconomic status and limited health literacy [110, 111].

Several tools (e.g., wearable devices) and smartphone applications are commercially available, which are decentralizing the role of self-driven lifestyle engagement. There has also been an increase in the use of continuous glucose monitors in people with type 2 diabetes to promote self-monitoring and facilitate self-regulation of lifestyle behaviors. However, the evidence regarding the reach, effectiveness, and long-term use of these tools and applications is limited. Further, securely sharing data and protecting privacy is still work under progress, which limits the widespread and full adoption of available technologies. Currently, best practices indicate only trusted technologies/telehealth platforms should be used, especially those that tailor advice to the person's engagement level, respond to health emergencies, and protect data privacy and security [112].

Finally, technology can also be used to foster healthcare-community linkages. For instance, websites can be used to publish lists of trusted education and support resources identified in the community [104], while geographic information

systems can be used to inform referral protocols [104]. Clinical decision support systems have been shown to improve patient referrals to community resources and achievement of diabetes treatment goals [104, 107, 113]. Communication technologies that automate patient referrals to community resources have been shown to improve provider referral rates and patient behavior [105] and should be considered to foster healthcare–community linkages to support diabetes lifestyle self-management.

Financing Lifestyle Diabetes Management

In this section, we examine the financing of interventions or strategies that support lifestyle management in people with diabetes through a crude lens. Delivering or covering the costs of lifestyle management programs or tools has an upfront cost; as such, these short-term investments must be balanced against potential benefits and returns. Much of this decision-making depends on how healthcare (and allied healthcare) services are financed and the perspective one is taking. At the level of the individual with diabetes, this decision is influenced by their current motivation, financial capabilities, and/or competing priorities.

From the perspective of the institution offering lifestyle management support services, some form of payment or reimbursement for them to provide this service is desired and/or required to remain financially solvent. From the perspective of the individual with diabetes, low-cost, high-value services or interventions with good outcomes and low side-effects are desired. This is especially true if the individual is also paying for the service or intervention, which is often the case in low- and middle-income countries where financial protections for healthcare (e.g., insurance) do not exist or are not widely used. This is also the case where the individual is the direct consumer of a product or tool (e.g., a wearable device or application) and is paying out of his/her/their disposable income for the promise of something that is supposed to facilitate a healthier lifestyle.

In the case of a third-party payer that "insures" healthcare service costs for individuals in a society—be this a government (e.g., the United Kingdom's National Health Service) or commercial stakeholders (e.g., private insurance companies)—a demonstration of the returns or the business case for investing in lifestyle management services or products are usually a prerequisite. The returns for third party payers are usually in the form of offsetting other high-cost healthcare expenditures like medicines, surgeries, or treating diabetes complications. This has been demonstrated in the LookAHEAD study, which showed lower need for blood pressure- and cholesterol-lowering medications among those receiving a lifestyle modification intervention [114]. This has also been recognized by the American Diabetes Association: based on the cost savings accrued from diabetes education and support services, the association recommends reimbursement by third-party payers for such services [49, 78]. However, the business case for each individual product and service available is currently limited.

The formal "business case" for lifestyle modification services has been developed and embraced by some healthcare systems and payers. Two examples include Discovery Health in South Africa and Kaiser Permanente, an integrated healthcare system and insurer in the United States. Both commercial corporations have adopted wellness into their healthcare insurance approach [115–117]. Either through calculating the potential cost offsets or as an embodiment of their mission and vision, these insurers have decided to cover the costs of wellness coaching for their members. In the United States, though these examples offer hope, the reality is that this vision is not ubiquitous and varies greatly by setting, perspective, and how health financing is set up.

Conclusion

Healthy lifestyles for diabetes self-management is a daily effort that takes place in a complex, multilayered system that includes the individual, the family, the community, and the healthcare system. Barriers that hinder effective lifestyle self-management may be encountered in each of these layers and the interaction of barriers may be different based on one's circumstances. Currently, the fragmentation of information and access across households, communities, and healthcare systems is itself a complexity that influences the likelihood that people with diabetes can engage in and maintain healthy lifestyles. As such, effective diabetes lifestyle management requires a coordinated effort focused on empowering individuals to ask about and adopt healthy lifestyle behaviors, providing ongoing support, and offering opportunities to succeed in the places where they live, play and work. This requires building efficient healthcare–community linkages, leveraging social support mechanisms, coordinating diabetes care, offering diabetes education and support resources in a variety of formats, sharing health information across settings, and financing strategies that support lifestyle modification services and referrals. Promising studies have already demonstrated the efficacy and effectiveness of clinical, community, broad societal strategies, and policies that can make lifestyle management more mainstream, accessible, and cost-effective. Such strategies should be widely adopted to realize the full potential of lifestyle management for improving the quality of life among those living with diabetes.

Multiple Choice Questions

1. The ABCD goals refer to control of:
   (a) Hemoglobin A1c and fasting blood glucose
   (b) Blood pressure and Cholesterol
   (c) Tobacco avoidance and Hemoglobin A1c
   (d) **Hemoglobin A1c, Blood Pressure, Cholesterol and Do not Smoke**
2. These are the first-line management recommendations for every person living with diabetes:
   (a) Insulin sensitizers
   (b) Low carbohydrate diet
   (c) **A healthy diet, regular physical activity, and avoiding tobacco smoking**
   (d) Injected insulin
3. Its purpose is to empower people with diabetes by giving them the knowledge, skills, and confidence to accept responsibility for their self-management.
   (a) Lifestyle modification
   (b) **Diabetes self-management and support**
   (c) Diabetes self-management support
   (d) Behavioral counseling
4. Diabetes self-management education and support should be offered at the following critical points:
   (a) At diagnosis
   (b) Annually or when treatment goals are not met
   (c) When transitions in care or life occur
   (d) **All of the above**
5. The physical activity guidelines for persons with diabetes recommend:
   (a) Adults with diabetes should engage in 300 minutes of moderate to vigorous intensity physical activity per week, spread over at least 3 days per week.
   (b) Adults with diabetes should engage in 150 minutes of vigorous intensity physical activity per week, spread over at least 3 days per week.
   (c) Adults with diabetes should engage in 150 minutes of light intensity physical activity per week, spread over at least 3 days per week.
   (d) **Most adults with type 2 diabetes should engage in 150 min or more of moderate- to vigorous-intensity aerobic activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity.**
6. This diet has been shown to be beneficial for people living with diabetes:
   (a) Low carbohydrate
   (b) High protein
   (c) Mediterranean
   (d) **All of the above**
7. These can be used for reminding, monitoring, and coaching people with diabetes to improve their lifestyle behaviors:
   (a) **Smartphone applications**
   (b) Counseling
   (c) Peer mentoring
   (d) Diabetes self-management and support
8. It is the process of giving patients control over their diabetes by equipping them with the knowledge, skills, and resources they need to self-manage their disease.
   (a) Motivation
   (b) Education and support
   (c) Behavior change
   (d) **Empowerment**
9. It involves the transfer of experiential knowledge about lifestyle behaviors or coping strategies between people who share a particular characteristic:
   (a) Guidance
   (b) Education
   (c) **Peer support**
   (d) Behavior change
10. Effective diabetes lifestyle management requires:
   (a) **Empowering individuals, providing ongoing support, and offering opportunities to succeed**
   (b) Providing insurance for diabetes management services
   (c) Involving families in diabetes management efforts
   (d) A prompt diagnosis and treatment regime

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Evidence and Implementation of Medical Nutrition Therapy in Persons with Diabetes

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Alison Evert, Melinda D. Maryniuk, and Jo-Anne Rizzotto

Abbreviations

A1C	Hemoglobin A1C
ADA	American Diabetes Association
AND	Academy of Nutrition and Dietetics
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DSMES	Diabetes Self-Management Education and Support
EAL	Evidence-Analysis Library
EBNPG	Evidence-Based Nutrition Practice Guidelines
MNT	Medical Nutrition Therapy
MUFA	Monounsaturated Fatty Acid
NCP	Nutrition Care Process
PUFA	Polyunsaturated Fatty Acids
RDN	Registered Dietitian/Nutritionist
SFA	Saturated Fatty Acids
US	United States

Introduction

The overall goal of the medical treatment plan is to provide the individual with diabetes the necessary tools to achieve glucose, lipids, and blood pressure within target ranges to prevent, delay, or manage the microvascular and macrovascular complications while minimizing hypoglycemia and excess weight gain. The foundation of any diabetes treatment plan for type 1 or 2 diabetes is healthful eating and regular physical activity. Due to the progressive nature of type 2 diabetes, the treatment plan that begins with lifestyle interventions and usually metformin will evolve over time to include glucose monitoring and changes in medications. For many individuals with type 2 diabetes, the treatment plan may eventually require insulin in order to meet individual health goals, whereas with type 1 diabetes lifestyle interventions, glucose monitoring, and insulin are all integral components of management plan from diagnosis, but whatever the treatment plan, nutrition interventions continue to be critical aspects of care [1, 2]. In addition to nutrition therapy provided by the registered dietitian nutritionist (RDN), a wide range of health professionals, such as registered nurses or pharmacists, can provide nutrition education in the context of a diabetes education program. Effective nutrition therapy may be implemented in individualized sessions or in a context of group education sessions. In fact, the American Diabetes Association (ADA) recommends that all individuals be offered an individualized nutrition care plan, preferably provided by a RDN [1].

Diabetes Nutrition Therapy: The Evidence

The Academy of Nutrition and Dietetics (AND), the largest association of nutrition professionals in the world, published evidence-based nutrition practice guidelines (EBNPG) for type 1 and type 2 diabetes in adults in their Evidence Analysis Library (EAL) and in print [3]. ADA have also published nutrition recommendations in the ADA Nutrition Therapy for Adults with Diabetes or Pre-diabetes: A Consensus Report and in the annual Standards of Medical Care in Diabetes [1, 4]. Multiple research studies support diabetes nutrition therapy as an effective tactic in achieving diabetes treatment goals. Medical nutrition therapy (MNT) provided by an RDN is also cost-effective [5].

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Based on the systematic review conducted by the AND, in adults with type 2 diabetes, MNT interventions implemented by RDNs resulted in significantly improved hemoglobin A1C (A1C) levels. In studies lasting 3 months, decreases from baseline A1C ranged from 0.3% to 2.0%; at 6–12 months reported decreases from baseline in A1C ranged from 0.3% to 1.8%. With ongoing MNT support for more than 12 months, continued decreases ranging from 0.6% to 1.8% were reported [3]. Although MNT interventions were effective throughout the disease process, the reduction in A1C was the greatest in studies in which participants were newly diagnosed with type 2 diabetes and/or had baseline levels > 8%. Studies have also demonstrated that ongoing RDN provided follow-up encounters ranging from three to six sessions, with a minimum of one follow-up session annually, can be helpful in maintaining glycemic improvements. During this time, it can be determined whether target goals can be achieved by implementation of MNT in combination with physical activity or whether medication(s) will need to be combined with MNT [3].

Regarding A1C outcomes in people with type 1 diabetes, MNT also contributed to significantly reduced A1C levels [3]. MNT provided by RDNs at 6 months reported that individualized MNT utilizing carbohydrate counting to optimize prandial insulin doses contributed to reduction in baseline mean A1C by 1.0% to 1.9%. Ongoing MNT resulted in sustained A1C reductions at 1 year and improved quality of life [6]. The landmark Diabetes Control and Complications Trial (DCCT) revealed that ongoing support of the RDN assisted in maintaining the mean A1C level at 6.9% in the intensive treatment arm throughout the 6.5 years of the study [7, 8]. There is strong evidence to support for individuals with type 1 diabetes to utilize the carbohydrate counting meal planning approach to adjust bolus (premeal) insulin doses (insulin-to-carbohydrate ratios) to desired carbohydrate intake. It should be noted, that these A1C reductions are similar or greater than what would be expected with treatment with currently available glucose-lowering medications for individuals with type 1 and 2 diabetes [1]. The key differences between nutrition therapy for people with type 1 and type 2 diabetes are summarized in Table 32.1.

Table 32.1 Nutrition Teaching Priorities

Type 1	Type 2
Glycemic management	Weight management; calorie reduction
Type and amount of carbohydrate	Glycemic management
Healthful eating patters	Healthful eating patterns
Fixed insulin regimen: carb consistency	Nutrient modifications (fat; sodium) based on co-morbidity risk (CVD, HTN)
MDII/Pump: flexible carb intake	Medication regimen and glucose monitoring drives degree of focus on carb type/amount.
Hypoglycemia prevention	Hypoglycemia prevention (based on medication)

In the systematic review published by AND, the effectiveness of MNT and cardiovascular disease (CVD) risk factors was also evaluated [3]. MNT was reported to have mixed effects on blood pressure and lipid profiles. The effectiveness of MNT may have been confounded by the 50% to 75% of the subjects that were noted to be taking antihypertensive and/or lipid-lowering medications. Additional long-term studies are needed at address the effectiveness of MNT on blood pressure and lipid profiles in adults with type 1 and 2 diabetes and disorders of lipid metabolism and hypertension.

Effective Nutrition Therapy Recommendations: Eating Patterns, Macronutrients, Weight Management, Fiber, Alcohol, Micronutrients/Herbal Supplements, and Weight Management

The 2019 ADA Nutrition Therapy for Adults with Diabetes and Pre-diabetes: A Consensus Report reviewed research studies of persons with diabetes following different types of eating patterns, including Mediterranean-style, vegetarian and vegan, low-fat, low-carbohydrate (26–45% total kcal) and very low carbohydrate (<26% total kcal/ketogenic diet), DASH (Dietary Approaches to Stop Hypertension), Paleo, and intermittent fasting [4]. The ADA Nutrition Consensus Report concluded that a variety of eating patterns are acceptable for the management of diabetes. It should be noted that an eating pattern represents the totality of all foods and beverages consumed, whereas an eating plan (or diet) is a guide to help individuals plan what, how much, and when to eat on a daily basis of the foods emphasized in the individual's selected eating pattern [9]. Personal preferences (e.g., tradition, culture, religion, health beliefs and goals, economics) and metabolic goals should be considered when implementing one eating pattern over another [4]. The eating pattern that the individual with type 2 diabetes chooses to follow will likely be the one that they will be able to follow long term [3]. Further research is needed to determine the most effective strategies to help persons with diabetes adopt new eating patterns. Refer to Table 32.2 for the eating patterns reviewed for ADA nutrition consensus report including a description of each eating pattern and list of potential benefits. Regardless of the eating pattern that the person chooses to follow, a variety of meal planning approaches such as carbohydrate counting, exchange lists for meal planning, or the plate method were implemented and effective. Meal planning approaches will be described in more detail later in the chapter.

While there has been ongoing research to define optimal levels of particular nutrients in diabetes nutrition therapy,

Table 32.2 Eating patterns linked with beneficial outcomes [4]

	↓DM	↓A1C	↓TG	↓CVD	↓Wt	↓LDL	↓BP	↑HDL	Incon-clusive
Mediterranean	✓	✓	✓	✓					
Vegetarian/Vegan	✓	✓			✓	✓			
Low-Fat	✓				✓				
Very Low-Fat					✓		✓		
Low-Carbohydrate		✓			✓		✓	✓	
Very Low-Carbohydrate		✓			✓		✓	✓	
DASH	✓				✓		✓		
Paleo									✓

Adapted from the ADA 2019 Nutrition Consensus Report

recent attention has focused on diet quality and the importance of a healthful eating pattern containing nutrient-dense foods with less focus on specific nutrients [10]. A recent meta-analysis linked high-quality diets (those rich in fruits and vegetables, whole grains, lean meats, legumes, nuts and seeds, dairy and low in processed foods, sugar sweetened beverages, and added fats and sodium) with a significant reduction in the risk of all-cause mortality, type 2 diabetes, and cardiovascular disease [11]. The 2021 Dietary Guidance to Improve Cardiovascular Health: A Scientific Statement from the American Heart Association reports that evidence from prospective observational studies has consistently identified an inverse association between diet quality and type 2 diabetes risk, and likewise, poor diet quality is also strongly associated with cardiovascular disease morbidity, and mortality [12].

Keeping that in mind, recommendations for an optimal macronutrient distribution for the management of diabetes continues to be a popular question. Although many research trials have attempted to identify the optimal percentages of macronutrients for a diabetes eating plan, review of the evidence reveals that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all persons with diabetes [1, 3, 4]. Total energy intake rather than the source of the energy is the priority, especially for individuals with type 2 diabetes. However, even total energy intake is determined by changes that the individual with diabetes is willing and able to make. The meal plan must take into consideration personal preferences and metabolic goals when recommending one eating plan over another [3].

Because macronutrients require insulin for metabolism and influence healthy eating, they still, however, must be discussed with the individual with diabetes. Although numerous factors influence glycemic response to foods, monitoring the carbohydrate intake whether by use of carbohydrate counting or experienced based estimation remains a key strategy in achieving glucose management [1, 3, 4]. Evidence exists that both the quantity and the type of carbohydrate eaten influence blood glucose levels; however, the total amount of carbohydrate eaten is the primary predictor of glycemic response. Day-to-day consistency in the amount of carbohydrate eaten at meals and snacks is reported to improve glycemic control, especially in persons on either MNT alone, glucose-lowering medications, or fixed insulin regimens. For selected adults with type 2 diabetes not meeting glycemic targets or where reducing glucose-lowering medications is a priority, reducing overall carbohydrate intake with low or very-low carbohydrate eating plans is a viable approach [4]. Most individuals within the United States report a moderate intake of carbohydrates (44–46% of total calories), and efforts to modify habitual eating patterns are often unsuccessful over time as people generally go back to their usual eating style [13]. Whereas in persons with type 1 or 2 diabetes who adjust their mealtime insulin doses or who are on insulin pump therapy, insulin doses should be adjusted to match carbohydrate intake [3, 4].

The ADA Nutrition Consensus Report also includes recommendations for adults with type 2 diabetes with overweight or obesity. The authors recommend that it is important to encourage reduced energy intake as part of an individualized diabetes eating plan, along with enhanced physical activity [3]. In people with type 2 diabetes, a 5% weight loss is recommended to achieve clinical benefit, and the benefits are progressive. The report also recommends the goal for optimal outcomes is 15% or more when needed and can be feasibly and safely accomplished. A systematic review of the effectiveness of diabetes MNT revealed mixed weight loss outcomes in participants with type 2 diabetes [3]. Therefore, in selected individuals with type 2 diabetes, the addition of glucose-lowering agents, weight loss agents that promote weight loss, or metabolic surgery can also be used as an adjunct to lifestyle modifications, to promote greater weight loss and maintenance goals, lower A1C, and reduce CVD risk [4]. The Look AHEAD study showed the feasibility of achieving and maintaining long-term weight loss in patients with type 2 diabetes, and many participants found using a

meal replacement product for one or two meals is particularly helpful in controlling intake and improving diet quality [14].

In addition to considering meal replacements, long-term success is associated with longer interventions (at least 16 sessions of group or individual counseling) that involves meal planning, increased physical activity (200–300 minutes/week), and behavior change strategies [15, 16]. The ADA recommends for patients who achieve short-term success that a long-term (>1 year) comprehensive weight maintenance program be prescribed [1]. An eating plan that results in energy deficit, behavioral strategies, and regular physical activity are critical components of any long-term weight loss and maintenance plan [15, 16]. Weight loss interventions can be provided in usual care settings and telehealth programs [4]. Healthcare providers can show their patients modest weight loss looks like in terms of a 5–10% decrease from their starting weight. This often makes it look much more achievable than if patients think they have to get down to a seemingly unattainable "ideal" body weight (see Table 32.3).

Over the years, strategies that restrict carbohydrate have been used for diabetes management and weight loss. The National Lipid Association Nutrition and Lifestyle Task force recently published a Scientific Statement providing a comprehensive review of the current evidence base available from recent systematic reviews and meta-analyses on the effects of low-carbohydrate and very-low-carbohydrate (including ketogenic) diets on body weight, glycemic control, lipoprotein lipids, and other cardiometabolic risk factors [17]. Based on the evidence reviewed, these diets may be linked with greater short-term (≤6 months) weight loss, but longer term (>6 months) results are equivalent to other dietary approaches for weight loss. The low-carbohydrate and very-low-carbohydrate diets may have advantages related to triglyceride reduction, appetite control, and reduction in the use of medication in management of type 2 diabetes. The evidence also revealed mixed effects on low-density lipoprotein cholesterol levels with some studies showing an increase. In addition, the authors reported no clear evidence for advantages regarding effects on other cardiometabolic risk factors based on their review. Long-term studies with clinic event outcomes are needed [4]. It should be noted that these diets are contraindicated in individuals with history of elevated triglycerides, pancreatitis, chronic kidney disease, disordered eating patterns, and pregnant women. Individuals with diabetes severely restricting carbohydrate are at increased risk of hypoglycemia if using insulin and/or insulin secretagogues and, therefore, should be medically supervised [17].

Table 32.3 Reasonable weight loss goals (5–10%)

Reasonable weight loss goals (5–10%)	
If you weigh	Then aim to lose
70 kg (154 lb)	3.5–7 kg (8–15 lb)
80 kg (176 lb)	4–8 kg (9–18 lb)
90 kg (198 lb)	4.5–9 kg (10–20 lb)
100 kg (220 lb)	5–10 kg (11–22 lb)
120 kg (264 lb)	6–12 kg (13–26 lb)
140 kg (308 lb)	7–14 kg (15–30 lbs)

Evidence is lacking to recommend a higher fiber intake for people with diabetes than for the general population. Thus, recommendations for fiber intake for people with diabetes are similar to the recommendations for the general public [3]. While diets containing 44 to 50 grams of fiber daily improve glycemia, more usual fiber intakes (up to 24 grams daily) have not shown beneficial effects [4]. The mean intake of dietary fiber in the United States is reported to be 17 g per day with only 5% of the population meeting the adequate intake (25 g for adult women and 38 g for adult men or 14 g total fiber per 1000 kcal) [18]. In addition, as with the general population, individuals with diabetes should consume at least half of all grains as whole grains [9].

For people with diabetes, evidence is also inconclusive to recommend an ideal amount of protein intake for optimizing glycemic control or improving CVD risk factors; therefore, protein recommendations should be individualized [1, 3, 4]. The amount of protein usually consumed by persons with diabetes is 15% to 20% of energy intake [19, 20], has minimal acute effects on glycemic response, lipids, and hormones, and has no long-term effect on insulin requirements [21].

Evidence is also inconclusive for an ideal amount of total fat for people with diabetes, and, therefore, goals should be individualized [1, 4]. The National Academy of Medicine has defined an acceptable macronutrient distribution of fat for all adults to be 20–35% [22]. The type of fat consumed is more important than total fat in terms of metabolic goals and influencing CVD risk, with the emphasis on decreasing saturated and trans fats and replacing them with unsaturated fats. Individuals should be encouraged, however, to moderate their fat intakes to be consistent with their goals to lose or maintain weight [17].

Plant-based foods rich in unsaturated fats (oils, nuts, avocados, fish) as a component of the Mediterranean-style eating pattern are associated with improved glycemic control and improved CVD risk factors in persons with type 2 diabetes [1, 4]. Benefits have been demonstrated from both monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFAs). Controversy exists on the best ratio of omega-6 to omega-3 fatty acids; however, PUFAs and MUFAs are both recommended as substitutes for saturated fatty acids (SFAs) or trans fatty acids. The amount of SFAs, cholesterol, and trans fat recommended for people with diabetes is the same as for the general population [9]. These recommendations include reducing SFAs to <10% of calories and limiting trans fat as much as possible. There is evidence from the general population that foods containing

omega-3 fatty acids have beneficial effects on lipoproteins and prevention of heart disease. Therefore, the recommendations for the general public to eat fish (particularly fatty fish) at least two times (two servings) per week is also appropriate for people with diabetes [9]. However, evidence from RCT does not support recommending omega-3 supplements for people with diabetes for the prevention or treatment of CVD despite evidence from observational and preclinical studies [1, 4].

Moderate amounts of alcohol ingested with food have minimum, if any, acute effect on glucose and insulin levels [23]. If individuals choose to drink alcohol, aim to limit daily intake to one drink or less for adult women and two drinks or less for adult men (one drink equivalent is equal to 12 oz beer, 5 oz of wine, or $1^1/_2$ oz of distilled spirits). Each drink contains approximately 15 g alcohol [4]. The type of alcoholic beverage consumed does not make a difference. The same precautions that apply to alcohol consumption for the general population apply to persons with diabetes. Abstention from alcohol is advised for people with a history of alcohol abuse or dependence; for women during pregnancy; and for people with medical problems such as liver disease, pancreatitis, advanced neuropathy, or severe hypertriglyceridemia.

However, alcohol consumption may place people with diabetes who take insulin secretagogues or insulin at increased risk for delayed hypoglycemia [23]. Consuming alcohol with food can minimize the risk of nocturnal hypoglycemia. Education and awareness of delayed hypoglycemia after consuming alcoholic beverages is important. Alcoholic beverages should be considered an addition to the regular eating plan for all persons with diabetes who choose to drink. No food should be omitted, given the possibility of alcohol-induced hypoglycemia and because alcohol does not require insulin to be metabolized [4]. In persons with diabetes, light-to-moderate amounts of alcohol (one to two drinks per day; 15 to 30 g of alcohol) are associated with a decreased risk of coronary heart disease, likely due to improved insulin sensitivity associated with alcohol consumption. Ingestion of light-to-moderate amounts of alcohol does not raise blood pressure or triglycerides, whereas excessive, chronic ingestion of alcohol does raise blood pressure and may be a risk factor for stroke [23].

No clear evidence has been established for benefits from vitamin or mineral supplements in persons with diabetes (compared with the general population) who do not have underlying deficiencies [1, 4]. Long-term metformin use is associated with vitamin B12 deficiency, suggesting that periodic testing should be considered [1]. There has been interest in prescribing antioxidant vitamins in people with diabetes, since diabetes may be a state of increased oxidative stress. Clinical trial data not only indicate the lack of benefit from antioxidants on glycemic control and progression of complications but also provide evidence of the potential harm [1, 24].

Therefore, routine supplementation is not advised. At this time, there is also insufficient evidence to support the routine use of micronutrients such as vitamin D, magnesium, and chromium, as well as use of herbs/supplements, or cinnamon for the treatment of diabetes [1, 3, 24]. In addition, herbal products are not standardized and vary in their content of active ingredients and have the potential to interact with and potentiate the effect of other medications. Therefore, it is important that individuals with diabetes report the use of supplements and herbal products to their RDN and/or healthcare provider. Without well-designed clinical trials to prove efficacy, the benefit of pharmacological doses of supplements is unknown, and findings from small clinical and animal studies are frequently extrapolated to clinical practice [3].

Individualization of the Nutrition Prescription and Eating Patterns

The first step in developing a meal plan for the person with diabetes is to base it on an individualized assessment [25]. The RDN will take a detailed history including an analysis of usual eating habits, past diets, comorbidities that affect nutrition, socioeconomic factors, cultural influences, and readiness to change in order to identify, collaboratively with the patient, the best approach to meal planning. Common approaches to meal planning with a RDN usually involve carbohydrate or calorie counting, developing sample menus, incorporating behavioral strategies such as mindful eating all while working within the eating preferences described by the patient such as a vegetarian eating style or avoiding certain food allergens. While a referral to a RDN is ideal, it may not always be realistic, and the physician is often in the position to get a patient started with basic meal planning recommendations. Thus, the physician or diabetes counselor should be prepared to ask a few key questions to help understand the patient's usual eating style and be better prepared to offer meaningful guidance. Suggested questions for an abbreviated assessment include:

- *What is your past experience with diet/meal plans?*
- *Tell me what you typically drink?(focus on learning if there are sources of significant carbohydrates from juices, sodas, or other sugar-sweetened beverages).*
- *Usual meal pattern (times/locations).*
- *How often do you eat vegetables—and what kinds?*
- *Tell me three things you think are going well with your eating pattern and three things you'd like to improve.*

Several eating patterns are associated with beneficial outcomes for people with diabetes and can be recommended by all members of the healthcare team [4, 26–29] (see

Table 32.2). No matter what eating pattern, aim for most food choices to focus on high-quality, minimally processed whole grains, vegetables, fruits, lean meats, seafood, legumes, nuts and seeds, dairy products and heart-healthy unsaturated fats and oils. As much as possible, aim to avoid sugar-sweetened beverages and minimize refined grain products, processed meats and added sugars, fats, and sodium.

The plate method has been used widely in many parts of the world as a useful method of controlling carbohydrate and calories without overwhelming patients with lists of foods and calculations of calories and carbohydrates. Recently, its effectiveness was demonstrated in research that randomized 150 adults with type 2 diabetes to either plate method approach or a carbohydrate counting approach. At 6 months, A1C improved within the plate method [−0.83% (−1.29, −0.33), $P<0.001$], and carbohydrate counting [−0.63% (−1.03, −0.18), $P = 0.04$] groups but not the control group [$P = 0.34$] [27]. Of particular interest were the additional benefits of the plate method seen in patients with lower literacy skills [27]. The ADA has created a variety of tools for healthcare providers to use in teaching patients the plate method [30] and it particularly useful for physicians, nurses, pharmacists and other non-dietitians to use when helping patients get started with meal planning. Note that the plate method can be adapted to meet the needs of multiple different cultural eating practices, using a bento box, bowl, or a banana leaf. No matter what is used to hold the food, guide the patient to identify the carbohydrate sources, and keep them limited to one section, with a similar size portion for protein foods and a larger serving allowed for nonstarchy vegetables.

Despite the effectiveness of the plate method, many patients ask for more specific guidance when it comes to carbohydrates and calories. Instead of giving a daily range for either, offering per-meal guidelines is more practical. Tables 32.4 and 32.5 offer such guidelines. In the United States, a carbohydrate (carb) serving is defined as the amount of food that yields 15 grams of carbohydrate. Thus, 1/3 cup cooked rice or pasta, ½ cup cooked oats, 1 oz slice bread, a small piece of fruit or 8 oz (240 mL) milk all have about 15 grams of carb. In other countries, the carb servings may be based on a portion size to yield a 10 gram carb serving. Quantities can be adjusted accordingly.

No matter what eating pattern is recommended, the success is due in large part to the patient's involvement in helping shape the meal plan, setting specific and realistic goals and participating in ongoing follow-up and systems of support. Ongoing support may be in the form of face-to-face visits, peer support, phone coaching, or even through the use of social media communities such as on Facebook that bring together people working together for a common goal. The healthcare provider will do well to identify resources within the community or online that can provide such support.

Table 32.4 Calories per meal: suggested ranges

Calories per meal: suggestedr		
Meal	Women	Men
Breakfast	300–400	400–500
Lunch	400–500	500–600
Dinner	400–500	500–600
Snacks	100–200	100–200

Table 32.5 Carbohydrate per meal: suggested ranges [31]

Carbs per meal—suggested ranges	
If you are male and not overweight	4–5 servings[a] 60–75 grams carb
If you are female and not overweight	3–4 servings 30–45 grams carb
If you are overweight (>10 lbs/4.5 kg)	Subtract 1 carb serving (15 grams)
If you exercise three to five times/week	Add 1 carb serving (15 grams carb)
Snacks	

[a]1 carb "serving is a portion of food equal to about 15 grams of carb such as one small apple, one small slice bread, 120 mL/4oz juice or 240 mL/8 oz milk

Conclusion

Nutrition therapy is a cornerstone of treatment for people with diabetes [31]. While the RDN is the person best qualified to develop an individualized meal plan, all healthcare team members have a role in giving patients guidance for healthy eating and ongoing support for the many behavior changes involved in maintaining dietary changes, especially those involved in weight management. Meal planning priorities and diet plans will vary based on type of diabetes, type of medications, other comorbidities, and multiple patient factors including usual eating habits and readiness to change. They will also change over time, making an annual assessment of nutrition needs and possible meal plan revisions important. In order to prepare to meet the client's nutritional needs, physicians and other healthcare providers will do well to identify dietitians with whom they can work collaboratively and/or mentor health educators or peer counselors to provide nutrition information for healthy eating using simple guidelines such as the plate method. And finally, remember that healthy eating for people with diabetes follows the same principles of what healthy eating is for everyone.

Multiple Choice Questions

1. For a person with newly diagnosed type 2 diabetes, what is a recommended weight loss goal?
   (a) 3%

(b) **5–10%**
(c) 15%
(d) 20%

2. Which of the following is a true statement about diabetes and alcohol?
   (a) People with diabetes should not drink alcohol.
   (b) Alcohol recommendations for serving size and amount are the same for both men and women.
   (c) **Hypoglycemia risk is increased in people taking insulin and/or insulin secretagogues.**
   (d) Alcohol is a good source of glucose.
3. What is the most important factor to consider when individualizing a meal plan for all people with diabetes:
   (a) Medical history and type of diabetes
   (b) Laboratory data and weight
   (c) Cultural background and food-related beliefs
   (d) Readiness to learn new behaviors and interest in changing old ones
   (e) **All of the above**
4. In the process of providing medical nutrition therapy for a person with diabetes, the goal is to improve overall diabetes control by:
   (a) Providing a written meal plan
   (b) Emphasizing portion control
   (c) **Individualizing the meal planning approach**
   (d) Using carbohydrate counting
5. For a person with type 1 diabetes who is using multiple daily injections of insulin, nutrition education priorities include all of the following, except:
   (a) Education on carbohydrate counting, flexible carbohydrate intake
   (b) Glycemic management
   (c) Hypoglycemia prevention
   (d) **Weight management, calorie restriction**
6. The American Diabetes Association recommendations include all of the statements except:
   (a) The amount of SFAs, cholesterol, and trans fat recommended for people with diabetes is the same as for the general population.
   (b) It is recommended that people with diabetes eat fish (particularly fatty fish) at least two times (two servings) per week.
   (c) **Omega-3 supplements should be recommended for people with diabetes for the prevention or treatment of cardiovascular disease.**
   (d) Plant-based foods rich in unsaturated fats as a component of the Mediterranean-style eating pattern are associated with improved glycemic control and improved CVD risk factors in persons with type 2 diabetes.
7. Your patient tells you she is taking supplements (such as cinnamon, antioxidants and Vitamin D) instead of making changes in her eating habits to manage her diabetes. The best response is:
   (a) "These products are a waste of money."
   (b) **"Micronutrients and herbal supplements may have the potential to interact with your prescribed medications, please bring them to your next appointment so we can evaluate them together."**
   (c) "Folk remedies like what you are describing don't ever work,"
   (d) "These are acceptable supplement's for people with diabetes to take as long as they are made by a reputable manufacturer"
8. Long-term metformin use has been shown to be associated with:
   (a) Iron-deficiency anemia
   (b) **Vitamin B12 deficiency**
   (c) Calcium deficiency
   (d) Weight gain
9. In adults with type 2 diabetes medical nutrition therapy (MNT) interventions implemented by RDN lasting longer than 12 months, resulted in significantly improved hemoglobin A1C levels:
   (a) 0.3%
   (b) 0.5–0.8%
   (c) **0.3–1.8%**
   (d) > 2.0%
10. Nutrition education priorities for type 2 diabetes include all the statements except:
   (a) Focus on the total energy intake rather than the source of the energy
   (b) Nutrient modifications (such as fat and sodium) based on comorbidity risk (such as cardiovascular disease and hypertension)
   (c) Changes in eating plan that the individual is willing to make
   (d) **Meal plan should include three meals and three snacks at specific times**

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Evidence and Implementation of Physical Activity and Exercise in Diabetes Mellitus

33

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Introduction

According to the World Health Organization (WHO), global health is influenced by three tendencies, (a) the aging of the population, (b) fast nonplanned urbanization, and (c) globalization, all of these resulting in unhealthy conducts and environments. As a consequence, noncommunicable diseases (NCDs) have increased in both high- and medium-income countries worldwide, accounting for 71% (41 million) of annual deaths which 4% (1.6 million) are attributable to diabetes mellitus, making it the fourth leading cause of death for NCDs [1–3].

Physical inactivity is considered the fourth attributable cause of mortality in the world.

Besides, behaviors like smoking and poor nutrition and excessive alcohol consumption are responsible for many of the diseases and the premature deaths related to chronic diseases [4]. Today physical activity (PA) is of great importance, since it has been correlated with health benefits and in the fight against the main NCDs, such as overweight and obesity, diabetes, hypertension, osteoporosis, cardiovascular disease and cancer. PA has also been found to be an important factor in maintaining mental health and socioemotional stability and improving the immune system [5–7].

The purpose of this chapter is to provide the physician with information on: (1) clarification of concepts related to human movement; (2) evidence of the benefits of PA and exercise in diabetes at the metabolic, enzymatic, molecular, muscular, immune, and mental levels; (3) effects of PA in relation to its intensity; (4) exercise prescription using the five A's model; and (5) finally a brief summary of the recommendations, indications, and contraindications of PA, in patients with diabetic complications.

Although the emphasis of this chapter is about the evidence and implementation related to physical activity and exercise, it should not be forgotten that this is just one part of the cornerstone of the treatment for diabetes mellitus, together with the nutritional and pharmacological aspects. However, nowadays it is agreed that diabetes management is multifactorial, and the health professional must be prepared to positively influence the change of behavior toward a healthy lifestyle and promote the physical, emotional, social, intellectual, spiritual, and occupational individual well-being, as well as improve the individual's physical fitness, quality of life (QOL), and metabolic control [8] (Table 33.1).

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Table 33.1 Physical activity and its relationship with lifestyle, exercise, and other common terms related to health and fitness

Physical activity						
Lifestyle				Exercise		
Wellness	Functionality	Quality of life	Health and disease	Physical performance	Fitness	Sports

Key Concepts About Physical Activity and Exercise

Human Movement

Represents a complex behavior that is influenced by personal motivation, health and mobility issues, genetic factors, and the social and physical environments in which people live [10].

Physical Activity

Caspersen and colleagues [11] were the first ones to define physical activity as "the bodily movement produced by the contraction of skeletal muscle that increases energy expenditure (heat) above the basal level." This generic definition for physical activity has endured during all these years and has been supported by different institutions and authors, having, maybe, the maximum exposure by the famous document supported by the US Secretary of Health in 1996, "Physical Activity and Health: Report of the Surgeon General." Since then, this landmark review of research on physical activity and health has been the basis for public policies in many countries [11].

Physical activity has four dimensions, which are type of activity, frequency, duration, and intensity of performing activity, and four domains, which are leisure, occupation, transport, and housework. Physical activity can either be classified as structured or incidental [12]. The first one can be considered exercise which is planned, with purpose, and promotes health. The incidental physical activity is not planned and usually is the result of daily activities at work and home or during transport [13].

There is another related term that has been frequently used to describe the physical activity type such as aerobic physical activity in which the body's large muscles move in a rhythmic manner for a sustained period of time. Aerobic activity, also called endurance activity, improves cardiorespiratory fitness. Examples include walking, running, swimming, and cycling. Based on the intensity of the activity, it can be classified as low, moderate, and vigorous physical activity (Table 33.2).

Table 33.2 Resume of physical activity classification based on METs, VO2máx, FCM, PSE, and intensity [9]

Intensity	METs	VO2máx (%)	FCM	PSE (6–20)
Behavior sedentary	<1.5	<37	<57	<9
Light	1.5–3.0	37–45	57–63	9–11
Moderate	3.0–6.0	46–63	64–73	12–13
Vigorous	>6	64–90	77–84	14–17

MET (metabolic equivalent of energy) is a common unit to express exercise intensity. One MET represents the resting energy expenditure during quiet sitting. *VO2max* maximum oxygen consumption, *FCM* maximum heart rate, *PSE* subjective perception of stress

Physical activity intensity is conceptualized as the rate of physical work performed by an individual and is expressed in terms of resting metabolic equivalents (METs). Maximal MET capacity is not certainly important by itself but becomes important when one considers the relative cost of a task or activity. Low physical activity includes light activities such as all incidental movements between >1.5 METs and < 3 METs; moderate physical activity (≥3–6 MET's); and intense or vigorous activity >6 MET's [14]. The greatest benefit of regular physical activity is the increase in physical work capacity (PWC), which is defined as the maximal rate at which a person can expend energy. On the other hand, physical inactivity is insufficient to meet current physical activity recommendations [15] (Table 33.2).

Exercise

It is a subcategory of physical activity where the activity is planned, structured, and repetitive, with the primary purpose of improving or maintaining physical fitness, physical performance, or health. "Exercise" and "exercise training" frequently are used interchangeably. Another used term is nonexercise activity thermogenesis (NEAT), which represents those activities of daily living other than exercise per se and includes such activities as sitting, standing, walking, and fidgeting [16].

Physical Fitness

Physical fitness has been defined as the ability to carry out a daily task with vigor and alertness, without undue fatigue

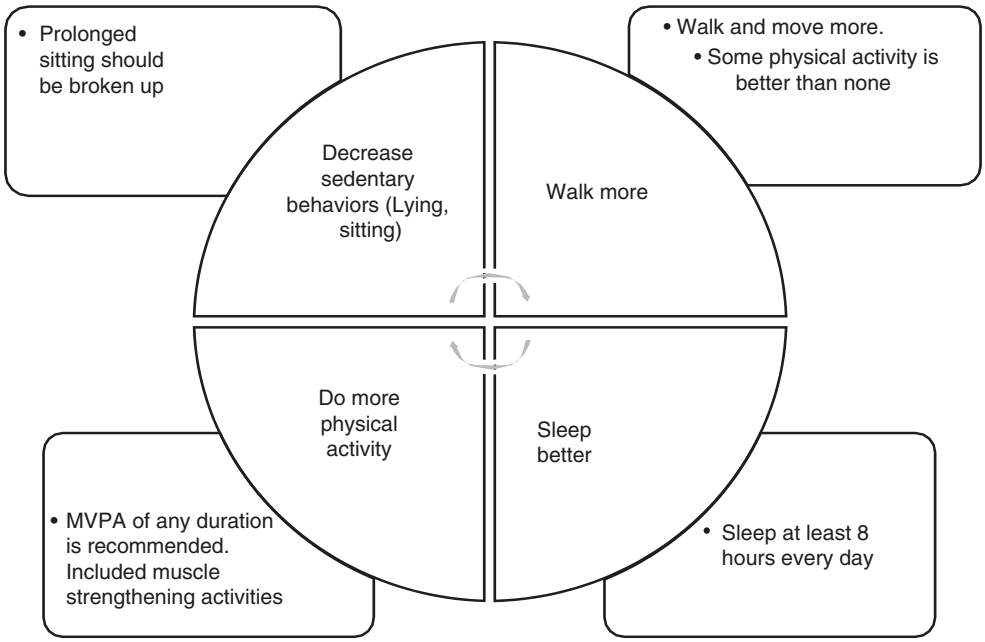

Fig. 33.1 Recommendations for physical activity/exercise in individuals with diabetes mellitus

and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies." The health-related components of physical fitness are (1) cardiorespiratory endurance, (2) muscular endurance, (3) muscular strength, (4) flexibility, and (5) body composition [11].

Sedentary Behavior

Sedentary behavior is considered as any activity that has an energy expenditure lower than 1.5 METs such as sitting, reclining, or lying posture (Tremblay, 2017). A group of experts sustains that sedentary behavior has an independent and qualitatively different effect on human metabolism, physical function, and health outcomes [16].

Physical Inactivity

Physical Inactivity is defined as noncomplying with the minimum international recommendations for PA for the health of the population [7].

As we can see, there are different concepts that are defined by energy expenditure or as a behavior (Fig. 33.1). All this terminology can be revised more profoundly at the "Terminology Consensus Project Sedentary Behavior Research Network" (SBRN) [17].

Evidence of Benefits of Physical Activity and Exercise on Diabetes Mellitus

This section addresses the benefits of physical activity and exercise related to metabolic, enzymatic, mitochondrial, endothelial, immunological, and mental disorders related to diabetes mellitus. Table 33.3 shows the different types of exercise (aerobic and resistance) that has found greater evidence to counter or reduce the incidence of complications from diabetes.

Aerobic and anaerobic exercise have positive effects in most metabolic parameter and in cardiovascular risk factors [25, 33, 34]. Some of the benefits are related to blood glucose control and HbA1c control (evidence level A), lipid profile improvement, reduction of systolic and diastolic blood pressure, reduction of body weight (level B) and adiposity [35], and lower total mortality rate (evidence C) [36, 37]. Recently, evidence shows that regular exercise can work as an antioxidant and as an anti-inflammatory factor [38, 39].

In the last years, resistance training has been shown to be beneficial in the metabolic management of the patient [40]. According to the American College of Sports Medicine, the recommendation is to perform muscle work (resistance exercise) consistently [41] (Table 33.4).

Another important benefit that has been shown is in the reduction of postprandial hyperglycemia, which is highly associated with complications of DM. Also, there is evidence that increasing exercise intensity has a higher reduction on blood glucose levels after meals [42] (Table 33.5).

Table 33.3 Summary of the main alterations and effects of diabetes in the body, as well as the benefits of physical activity and the type of exercise recommended

Type of exercise	Disorders	Effects of disorders	Benefits of physical activity and exercise on alterations	Evidence of benefits of physical activity and exercise
	Enzymatic			
Resistance	PFK1 –M deficiency	The deficiency of the enzyme PFK1 M leads to alterations in the action or secretion of insulin, which can be a risk factor for developing diabetes mellitus [18].	The adoption and maintenance of PA are important aspects for the control of glucose, the action of insulin and the reduction of risk of developing DM [19].	Qadir, et al. (2021). Effectiveness of resistance training and associated program characteristics in patients at risk for type 2 diabetes: a systematic review and meta-analysis.
Aerobic	Glycogen synthase (GS)	People with IR have shown an alteration in insulin signaling and a reduction in glycogen synthase, affecting muscle glycogen synthesis [19].	Exercise promotes an increase in GS affinity for glucose [20].	Jensen, et al. (2013). Effect of acute exercise on glycogen synthase in muscle from obese and diabetic subjects.
	Metabolic			
Aerobic	Hyperglycemia	Chronic exposure of cells to high glucose levels favors the development of microvascular conditions in the patient [21].	Muscle contraction increases insulin-independent glucose uptake through the translocation of GLUT-4 to sarcolemma and T tubules [22].	Gao, et al. (2021). The therapeutic effects of mild to moderate intensity aerobic exercise on glycemic control in patients with type 2 diabetes mellitus: A meta-analysis of randomized trials
Aerobic	Insulin resistance	Insulin resistance (IR) alters the elimination of glucose, resulting in a compensatory increase in insulin and hyperinsulinemia. In addition, IR increases metabolic changes as dyslipidemia, arterial hypertension and endothelial dysfunction [23].	The sustained activation of AMPK, GS, increased expression of GLUT-1, GLUT-4 and hexokinase II, facilitate the resintesis of muscle glycogen by glucose uptake and by insulin sensitivity [21].	Tarabi et al., (2015). The Effect of 8 Weeks Aerobic Exercise on Insulin Resistance in Type 2 Diabetes: A Randomized Clinical Trial
Aerobic	Metabolism of lipoproteins	Increase in triglycerides and reduction in high-density lipoprotein (HDL), increasing the risk of dyslipidemia [24].	Exercise increases the ability of skeletal muscle to use lipids as an energy source instead of glycogen. In addition, it has been shown that aerobic PA increases HDL levels, affecting the reduction of developing dyslipidemia [25, 26].	Wang et al. (2017). Effects of aerobic exercise on lipids and lipoproteins.
	Mitochondrial functions			
Aerobic	Formation of reactive oxygen species (ROS)	Oxidative stress in the blood vessels and beta cells of the pancreas. Accumulation of mitochondrial damage promotes the aging process and affects the beta cells of the pancreas resulting in insufficient insulin synthesis [21].	Exercise-induced ROS generation results in increased activity of antioxidant enzymes (SOD, catalase glutathione peroxidase) and nonenzymatic antioxidants (coenzyme Q10, glutathione, lipoid acid), which subsequently lead to increased resistance to oxidative stress [27].	Simioni et al. (2018). Oxidative stress: role of physical exercise and antioxidant nutraceuticals in adulthood and aging
	Endothelial			
Aerobic	Vascular injury	Circulating endothelial cells facilitate the formation of atherosclerotic plaques due to the high flow of free fatty acids in insulin-resistant tissues. This condition is considered a risk factor for the development of macrovascular conditions [21].	It improves vascular function, including the production and bioavailability of endothelium-derived substances such as NO, which are antiatherogenic. Exercise also influences arterial structure, including external remodeling that increases the arterial diameter [28].	American Diabetes Association. (2016). Physical activity/exercise and diabetes: A position statement of the American Diabetes Association
	Immunological			

Table 33.3 (continued)

Type of exercise	Disorders	Effects of disorders	Benefits of physical activity and exercise on alterations	Evidence of benefits of physical activity and exercise
Aerobic	Inflammatory markers	Chronic inflammation favors the presence of inflammatory markers (IL-1, IL-2, IL-12, IL-18, TNF-α) decreases the action of NK cells and the expression of antioxidant genes. Which results in the patient with DM being more susceptible to getting sick [21, 29].	It stimulates the secretion of anti-inflammatory cytokines IL-10 and TGF-β, responsible for inhibiting inflammatory cytokines. There is also an increase in leukocytes, neutrophils, killer natural cell, and lymphocytes [27].	Nieman, et al. (2020). Exercise immunology: Future directions. Da Silveria et al., (2020). Physical exercise as a tool to help the immune system against COVID-19: an integrative review of the current literature
	Mental			
Aerobic	Depression	People with DM have recorded a lower value of brain-derived neurotrophic factor (NFBD), which may be a factor in the development of neurovascular conditions. In addition, it has also been correlated between decreased BDNF and depression [30, 31].	PA optimizes the level and function of the neurotransmitter system (e.g., glutamate, GABA, serotonin, dopamine, and noradrenaline) in turn, changes in neurotransmission mediate changes in the expression of the BDNF gene in various regions of the brain (e.g., hippocampus, nucleus accumbens, and amygdala) [32]	Phillips et al., (2017). Brain-Derived Neurotrophic Factor, Depression, and Physical Activity: Making the Neuroplastic Connection.

Table 33.4 Abbreviations

DM	Diabetes mellitus
PFK1–M	Phosphofructo-1-kinase/muscle subtype in humans.
PA	Physical activity
IR	Insulin resistance
GS	Glycogen synthase
SOD	Superoxide dismutase
NO	Nitric oxide
IL-1	Interleukin-1
IL-2	Interleukin-2
IL-12	Interleukin-12
IL-18	Interleukin-18
TNF-α	Tumor necrosis factor alpha
NK cells	Natural killer cells
TGF-β	Transforming actor of beta growth
NFBD	Brain-derived neurotrophic factor
GABA	Gamma-aminobutyric acid

Table 33.5 Summary of the evidence of the percentage of changes and benefits of exercise in the different metabolic, cardiovascular mortality in individuals with diabetes mellitus

Component	Effect	Level of evidence
Blood glucose control	(a) Aerobic exercise: Decreases blood glucose 57 mg/dL (b) Resistance: Decreases blood glucose 10 mg/dL	A
HbA1C control	(a) Aerobic exercise: Decreases HbA1c between 0.4 to 1.2% (0.66% average). (b) Resistance exercise: Decreases HbA1c 0.3%. (c) Combined: Decreases HbA1c 0.34%.	A

Table 33.5 (continued)

Component	Effect	Level of evidence
Serum lipid profile	(a) Aerobic exercise: Decreases total cholesterol from 23 mg/dL a 0; LDL decreases from 14 mg/dL a − 1.1 mg/dL with a 6.4 mg/dL average; HDL increases 5 mg/dL or an increase compared with basal of 12%; triglycerides showed no change (b) Resistance exercise: Total cholesterol decreased 3 mg/dL; LDL decreased 6 mg/dL; HDL increased 1 mg/dL	B
Reduction of SBP and DBP	(a) Aerobic exercise: SBP decreases in average 19 mmHg. DBP decreases 8 mmHg. (b) Resistance exercise: SBP decreases an average of 20 mm hg. DBP decreases 13 mmHg.	B
Reduction of body weight, primarily body fat	(a) Performing 1 hour of moderate aerobic exercise reduces body fat [7, 16]; individuals who maintain weight loss for at least 1 year typically perform approximately 7 hours per week of moderate to vigorous exercise intensity	B
Reduction of mortality	(a) It has been shown that exercise is associated with a 1% reduction of HbA1c levels; this is associated with a decreased risk of cardiovascular events in 15–20% and 37% of microvascular events due to this; exercise could reduce mortality by these events Observational studies suggest that the greater the physical activity, the lower the risk of global mortality. Additionally, exercise improves cardiopulmonary efficiency and physical and mental health	C

The Importance of the Intensity Levels of Activities/Exercise in Patients with Diabetes Mellitus

Physical activity intensity (low, moderate, and vigorous) is an essential variable on exercise prescription to improve specifics health and physical fitness parameters (2). Table 33.6 shows the principal criteria and the used definitions to categorize each intensity.

Low Intensity

Low intensity activities are considered as the one that expend between 1.5 to 3 METS. There is strong evidence of an inverse dose-response relationship between physical activity and the risk of type 2 diabetes. Risk reductions are observed with up to 5–7 hours of low-intensity physical activity and leisure time [43].

Is important to mention that replacing 30 minutes of sedentary behaviors with the same amount of time with low level intensity activities has an association with the reduction from 6% to 31% risk of DM2 [44].

Moderated Intensity

Moderate intensity physical exercise stimulates cellular immunity through the secretion of anti-inflammatory cytosins such as IL10 and TGF-β, responsible for inhibiting inflammatory cytosine. There is also an increase in leukocytes, neutrophils, natural killer cells and lymphocytes [27, 29].

Table 33.6 Intensity of activities in patients with Diabetes Mellitus

Intensity	MET	Activities
Low	1,6 a < 3	*Recreational cycling 6 mph *Home activities (dusting, straightening up, changing linen, carrying out trash) *Car wash and wax *Hatha yoga *Stretching exercises
Moderate	3 a < 6	*Lawn mowing *Running 4mph *Golf *Walk with the dog *Swimming
Vigorous	6 a < 9	*Running 5mph *Play basketball *Play tennis *Mountain biking *Fitness classes

Table 33.7 FITT for people with diabetes

	Aerobic	Anaerobic resistance	Anaerobic resistance
Frequency	3–7 days a week.	2–3 days a week.	≥2–3 days a week.
Intensity	Moderate to vigorous*	Moderate to vigorous*	Slight discontent
Time	150 min/week at moderate to vigorous intensity.	1 to 3 series of 10 to 15 repetitions. 8 to 10 exercises.	8–10 exercises with 1–3 series of 10 to 15 repetitions
Type	Activities using large muscle groups.	Body weight, resistance bands, or resistance machines	Static or dynamic
Suggestions for safe practice of exercise	Monitor your blood glucose level before and after the exercise session. Avoid muscle contractions or physical work in the body area where insulin has been given. Avoid physical activity in the afternoon or evening, or with the peak of action of the medication. Doing exercise with someone else. Stay hydrated.		

* Moderate aerobic intensity 64% to 73% maximum heart rate
* Vigorous aerobic intensity 77% to 84% maximum heart rate
* Moderate anaerobic resistance 50–60% 1 RM
* Vigorous anaerobic resistance 70–85% 1 RM

Vigorous Intensity

High-intensity exercise in the HIIT modality has been shown to reduce hyperglycemia and postprandial hyperglycemia in patients with type 2 diabetes mellitus [45]. It also increases metabolic health [46].

Physical Activity Recommendations for People with Diabetes

The recommendations for the diabetic patient on physical activity and exercise are the ones proposed by the American College of Sports Medicine [47] and are summarized in Table 33.7.

But what do we have to recommend? This is an important question that has to be answered based on main principles: first, people have to move more; second, they need to be more active; third, they have to decrease their sedentary behaviors, and eventually, they will be able to improve their fitness by doing more exercise, control their diabetes, and perform a sports activity. In summary, we cannot run if we cannot learn to walk first. The secondary principle would be that the practice of physical activity should be a joy, a real desire to do it for pleasure, or a well-being that causes it and what is associated. Therefore, physical activity recommendations should not be considered as something mandatory to comply instantly and not a rule for all goals [7].

Based on this argument, all the recommendations of physical activity particularly in individuals with diabetes should promote healthy lifestyles, wellness (physical, emotional, social, intellectual, spiritual, occupational), improved fitness [48], improved functionality, and quality of life (QOL) [49], but also, we should limit physical inactivity [8], avoid sitting for a prolonged time [50], walk more [51], and sleep better (Fig. 33.1).

Note: Adapted from the recommendations of the 24 hours of movement (in Tremblay, MS., et al. "Canadian 24-hour movement guidelines for children and youth: an integration of physical activity, sedentary behaviours, and sleep." *Applied Physiology, Nutrition, and Metabolism* 41.6 (2016): S311–S327: and adjusted to the recommendations for adults from the WHO 2020. (In:Bull, FC., et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviours. British journal of sports medicine, 2020, vol. 54, no 24, p. 1451–1462.

Counseling, the Five A's, and Motivational Interviewing

How to prescribe exercise in people living with diabetes? Caring for the individual with diabetes mellitus through the prescription of exercise has been reported to achieve metabolic control and limit the development of macro- and microvascular complications [52]. Besides, this, studies suggest the need for a larger volume of physical activity for decreasing the cardiovascular risk factors of patients with diabetes. In this situation, prescribing the correct dose of exercise becomes necessary [53]. An exercise prescription consists of mode (type), frequency, intensity, duration, and progression. Determining the appropriate mode depends upon patient preference and safety issues regarding the state of T2DM or other conditions. Frequency, intensity, and duration are specific to the type of activity and should be tailored to the patient's abilities to perform the activity safely. The health professional should address periodic progression to maintain the exercise stimulus needed to promote continued health improvements and prevent "plateauing." Based on the current scientific research [54, 55], this chapter proposes recommendations that enable healthcare professionals to advocate for their patients with T2DM by offering safe and effective treatment options and decreasing the noncompliance to exercise recommendations. It is necessary to use a systematic process in the care and management of individuals with diabetes. Evidence shows that lifestyle counseling in primary care is strongly associated with rapid control of glycosylated hemoglobin, blood pressure, and lipid profile [56]. The clinical evaluation to prescribe that the patient with diabetes mellitus first complies with the recommendations of physical activity and then with indicating physical exercise with the intention of improving their metabolic control, reducing risks for exercise, and adapting their limitations requires a systematic process that helps us cover all these aspects. The concept of formed exercise prescription was previously defined to have the following components: written, structured advice on exercise with details of frequency, intensity, type, timing, and progression [57] (Table 33.8).

Table 33.8 Wellness screening for physical activity and exercise recommended in patients with DM. Note: Based and adapted from ACSM's Guidelines for Exercise testing and Prescription. American College of Sports Medicine. 7th edition. 2006

Characteristic	Results
Lifestyle assessment • Use of drugs, tobacco, alcohol, • Sleep. • Leisure activities. • Moving activities. • Mental health. • Physical activity patterns and sedentary behaviors. • Assessment of perceptions about nutrition and physical activity (from 1 to 10: How important is the physical activity for your health? And how important is for you to be active everyday?	
Levels of physical activity and energy expenditure • Assess the level of physical activity with the IPAQ questionnaire (IPAQ, international physical activity questionnaire), • Calculation of energy expenditure (intake/expenditure).	
Risk for physical activity • PAR-Q the physical activity readiness questionnaire for everyone. • Risk presence questionnaire. • Applying the ACSM preparticipation screening algorithm.	
Physical activity (PA) behaviors • Behavior change level or stage questionnaire. • Self-efficacy and self-determination for PA, • Barriers and facilitators to physical activity.	
Medical • Postural angles of skeletal structure. • Body composition nutritional status. • Laboratory profile (kidney function, visual capacity, EKC electrocardiogram, dysautonomic complications).	

Because one of the most frequent complications in individuals with DM is cardiovascular complications, it is important to apply the algorithm of recommendations for exercise preparticipation health screening of the American College of Sports Medicine ACSM [58].

A systematic method of approaching the patient with diabetes is required to prescribe exercise safely. One of the practical processes to perform the proper prescription of the exercise is to apply to counsel using the five A's (Fig. 33.2). Studies show that educating the patient through counseling is effective but will depend on who performs it and how they perform it [59]. Counseling is defined as the methodical and systematic process to change from behaviors to healthy behaviors in individuals.

The objective of applying the counseling is to comply with goals. This process determines the patient's proposed goals, which are defined by the clinical evaluation findings.

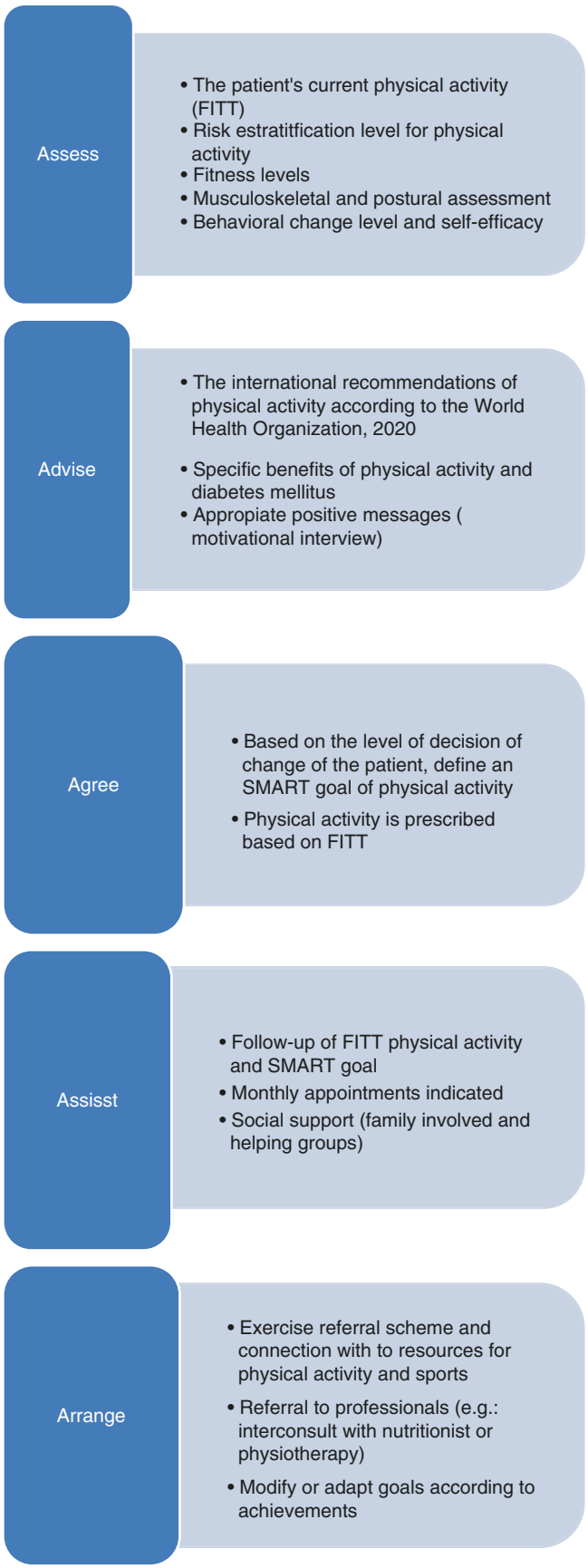

Fig. 33.2 Elements of physical activity counseling using the five A's model and emphasized the SMART goals (acronym of Specific, Measurable, Achievable, Reliable, and Time-bound) and FITT characteristics of physical activity: (Frequency, Intensity, Type, and Time of exercise or physical) activity. Note: Adapted from the five A's by Glasgow RE, Emont S, Miller DC. Assessing delivery of the five "As" for patient-centered counseling. Health Promot Int. 2006;21(3):245–55. The description of each A is adapted from: Meriwether RA, Lee JA, Lafleur AS, Wiseman P. Physical activity counseling. Am Fam Physician. 2008;77(8)1029–1136

The process to set these goals is known as SMART Goals, an acronym for Specific, Measurable, Achievable, Realistic, and Timely.

Experiences tell us that the approach of the individual with diabetes is to work with the behaviors and can be based on the motivation to exercise or be more active. One of the techniques that work for behavior change is motivational interviewing (MI). At primary care, it can be a motivational strategy for the individual to achieve effective changes in their control. Besides this, the purpose of MI in individuals with diabetes is to understand the reasons patients have to address their physical inactivity and build and strengthen their motivation to change this aspect. Why it has worked in diabetes management is because it is recognized that MI is patient-centered and establishes that behavior change is the patient's responsibility, is influenced by the motivation it receives, and by the beneficial changes it is presenting [60, 61].

Finally, exercise prescription activities through support groups are also equally effective for the metabolic control of patients since the influence of others with the same condition strengthens healthy behaviors. In addition, in the group activities, educational and exercise workshops have been applied that favor the control of the disease. In this sense, the workshop occupies a predominant role as a precursor of behavioral changes. A workshop is defined as a work methodology that integrates theory, technique, and practice, in which the three elements mentioned are fed back and improved continuously. It is a modality where the theoretical and technical knowledge acquired is applied consciously and assimilates relevant concepts and principles that put them into practice. In summary, the workshops are an important alternative that allows a closer insertion in the real world [62, 63].

We can summarize that exercise counseling can have many steps, which can help to approach the person con diabetes.

Exercise in the Presence of Specific Long-Term Complications of Diabetes

Diabetic Retinopathy The patients with retinopathy should be screened to have a well-defined stage of the disease from nonproliferative (NPDR) to proliferative (PDR) degeneration. With patients with NPDR, we should avoid physical activities that can dramatically increase blood pressure, such as powerlifting. On the other hand, patients with PDR should avoid vigorous aerobic or resistance exercise because of the risk of triggering vitreous hemorrhage or retinal detachment; we must avoid vigorous exercise; jumping, jarring and head-down activities, and breath holding [64]. By other hand, breathing exercises are highly recommended.

Peripheral Neuropathy Decreased pain sensation in the extremities results in an increased risk of skin breakdown and infection and of Charcot joint destruction. This is why some prior recommendations have advised nonweight-bearing exercise for patients with severe peripheral neuropathy. Regular aerobic exercise may also prevent the onset or delay the progression of peripheral neuropathy in both type 1 and type 2 diabetes. Studies have shown that moderate-intensity walking may not lead to an increased risk of foot ulcers or re-ulceration in those with peripheral neuropathy [65]. Physical activities like swimming, cycling, chair exercises, arm exercises, and everything that does not require the feet are the most recommended in these patients (moderate weight-bearing exercise). Proper care of the feet is needed to prevent foot ulcers and lower the risk of amputation; keep feet dry and use appropriate footwear, silica gel or air midsoles, and polyester or blend socks (not pure cotton); **Autonomic neuropathy** can increase the risk of exercise-induced injury or adverse events through decreased cardiac responsiveness to exercise. Autonomic neuropathy is also strongly associated with cardiovascular disease in people with diabetes. The patient's symptoms are postural hypotension, impaired thermoregulation, impaired night vision due to impaired papillary reaction, and unpredictable carbohydrate delivery from gastroparesis predisposing to hypoglycemia, which should be recognized before you recommend exercise. People with diabetic autonomic neuropathy should be screened and should receive physician approval and possibly an exercise stress test before embarking on physical activity levels more intense than usual because this may cause postural hypotension, chronotropic incompetence, delayed gastric emptying, altered thermoregulation, and dehydration during exercise. Low-intensity exercises that do not modify blood pressure such as water activities, stationary bike, and seated exercises are some physical activity recommendations. Patients with postural hypotension must avoid activities with rapid postural or directional changes to prevent fainting or falling. Cardiac autonomic neuropathy patients should have a physician approve and possibly undergo symptom-limited exercise testing before exercise. Patients with blunted heart rate response use heart rate reserve and ratings of perceived exertion to monitor exercise intensity. In general, autonomic neuropathy people should avoid exercise in hot environments and hydrate well [66, 67].

Chronic Kidney Disease Physical activity can acutely increase urinary protein excretion. Vigorous exercise should be avoided the day before urine protein tests are performed to prevent false-positive readings [2]. Both aerobic and resistance training improve physical function and quality of life in individuals with kidney disease, all activities can be beneficial, but exercise should begin at a low intensity and vol-

ume if aerobic capacity and muscle function are substantially reduced; avoid exercises that sharply increase blood pressure: violent physical activities, Valsalva maneuvers, and lifting weights.

Exercise increases physical function and quality of life in individuals with kidney disease. Supervised, moderate aerobic physical activity undertaken during dialysis sessions may be beneficial and increase compliance. We must emphasize hydration and blood pressure control; electrolytes should be monitored when exercise is done even more during dialysis sessions [68].

Cardiovascular Diseases We can include some diseases in this category like coronary artery disease, exertional angina, hypertension, myocardial infarction, stroke, and peripheral artery disease. For coronary artery disease, coronary perfusion may actually be enhanced during higher intensity aerobic or resistance exercise; all physical activities are okay; consider exercising in a supervised cardiac rehabilitation program, at least initially. Congestive heart failure is most commonly caused by coronary artery disease and frequently follows a myocardial infarction. In this scene, the recommendation is to avoid activities that cause an excessive rise in heart rate and focus more on doing low or moderate-intensity activities. In Peripheral artery disease, lower extremity resistance training improves functional performance; low or moderate-intensity walking, arm ergometer, and leg ergometer preferred as aerobic activities are recommended [69].

Summary

- Patients with possible cardiovascular (CV) disease, microvascular, neuropathy, or nephropathy complications and should undergo a medical evaluation, which will include medical history, physical examination (including eye screening examination, foot examination, and neuropathy detection), resting EKG and possibly stress test.
- The stress exercise test should be performed in all patients considered with high risk for CV disease and for the dose of exercise prescription, for risk stratification, to detect silent coronary disease and to detect abnormal hypertensive responses.
- It is highly recommended to give a follow-up of the diabetes complications.

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Part VI

Drug Therapy

The "Old" Oral Antidiabetics

34

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Introduction

Treatment of patients with type 2 diabetes aims to avoid acute symptoms of hyperglycemia and to prevent macro- and microvascular complications. In recent years, the number of glucose-lowering drugs increased to unprecedented levels. The American Diabetes Association (ADA) lists seven drug classes of available glucose-lowering agents in the last edition of their standards of medical care in diabetes [1]. All are proven to decrease HbA1c-levels or postprandial glucose excursions, but evidence on patient-relevant outcomes, such as cardiovascular mortality, amputations, or retinopathy, is sparse. Reduction of HbA1c-values is often used as a surrogate outcome measure to assess the efficacy of antidiabetic medication. However, its appropriateness has been disproven [2, 3]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [4, 5] and the Veterans Affairs Diabetes Trial (VADT) [6, 7], a rigid treatment regime with low HbA1c-targets did not result in better patient-relevant outcomes. Patients in the intervention arm of the ACCORD study even had a higher risk of mortality, and consequently, the study was terminated earlier [4]. Other drugs have been withdrawn from the market because of a negative benefit-risk ratio, for example, phenformin, which increased the risk of lactic acidosis or rosiglitazone that reduced HbA1c-values but increased cardiovascular risk [8]. In recent years, pharmaceutical companies decided to withdraw several new antidiabetic agents from the German market, such as vildagliptin and canagliflozin, because no additional benefit over usual care could be demonstrated and therefore health insurances would not have covered additional costs.

In 2012, the ADA and the European Association for the Study of Diabetes (EASD) recommended patient-centered care including shared decision-making (SDM) [9] and reasserted this position in further statements [10]. SDM is a particular form of communication between patients and their health care professionals. It focuses on the mutual exchange of information in order to involve patients in the decision-making process [11]. Therefore, patients need understandable information on probabilities of benefits and harms of treatment options [12–14]. The question to be answered is, what option is the best to prevent diabetes-related complications and yet in line with individual patient values and preferences? Supportive tools in that process are patient decision aids, which help patients to weigh up pros and cons of diabetes treatment [15, 16].

This chapter gives an overview of older classes of antidiabetic agents and their efficacy. It is based on a systematic inventory published in 2015 and updated in the first edition of The Diabetes Textbook [2]. Sulfonylureas (SU) and biguanides are the oldest classes of oral glucose-lowering agents. Later, thiazolidinediones (TZDs), alpha glucosidase inhibitors (AGIs), and meglitinides were approved. Table 34.1 shows the old drug classes and their compounds that are still available in the United States or Europe. Newer classes, such as sodium-glucose cotransporter 2 (SGLT-2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors, will be described in other chapters of this book.

According to recent guidelines [1, 7, 14, 17], this chapter focuses on the efficacy of metformin and SU monotherapies compared with other monotherapies as well as comparisons of metformin-based combinations. At the end of this chapter, we give an example of our decision aid for patients with type 2 diabetes and how diabetes educators share evidence-based information with their patients [18–20].

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Table 34.1 Overview of older classes of antidiabetic agents[a]

Class	Compounds[b]	Mechanism of action
Biguanides	• Metformin	Multiple sites of action. Not fully understood. Increase of insulin sensitivity by increasing peripheral glucose uptake, decrease of intestinal glucose absorption, and decrease of hepatic glucose production
Sulfonylureas (SU), second and third generation	• Glyburide (Glibenclamide) • Glimepiride • Glipizide • Gliclazide	Stimulation of insulin release in pancreatic beta cells. Decrease in hepatic clearance of insulin. Additional extra-pancreatic mechanisms of actions have been described
Thiazolid-inediones	• Pioglitazone • Rosiglitazone (withdrawn from many markets)	Reduction of insulin resistance in target cells through transcription of several genes involved in glucose and lipid metabolism
Alpha glucosidase inhibitors (AGI)	• Acarbose • Miglitol	Inhibition of alpha-glucosidase, which delays intestinal degradation of complex carbohydrates and thus prolongs post-prandial glucose absorption
Meglitinides	• Nateglinide • Repaglinide	Stimulation of insulin release in beta cells. Rapid acting stimulation. Weaker binding affinity and faster dissociation than SU

[a]Adapted from [2]
[b]Available in Europe (EMA) or the US (FDA) [1]

Methods

We updated our search from April 2014 [2]. In a first step, we searched PubMed and the Cochrane library for systematic reviews and meta-analyses published from May 2014 to the end of November 2021. Systematic reviews were considered if they included randomized controlled trials on the efficacy of metformin, sulfonylureas, thiazolidinediones, meglitinides, or alpha-glucosidase inhibitors as monotherapy or combination of two or three drugs. There is a growing number of network analyses. They typically comprise indirect comparisons when there is no head-to-head comparison available. Network analyses are methodologically challenging and can lead to false results and interpretations if differences between studies were not adequately considered [21]. Treatment of type 2 diabetes is complex, and as a result, RCTs in meta-analyses are usually heterogeneous. We therefore excluded network meta-analyses. In addition, inclusion criteria, such as study duration, sample size, target group, and drug classes, vary between systematic reviews. Hence, following our previous methodological approach [2], we extracted RCTs from the reviews that fulfilled our inclusion criteria: (1) patient-relevant primary endpoint, that is, macro- and microvascular complications, cardiovascular mortality, total mortality, and quality of life; (2) intention-to-treat analysis; (3) follow-up of at least 24 weeks and adequate sample size; and (4) hard clinical endpoints that had to be reported. Finally, we searched for further studies and screened the websites of the National Institute for Health and Care Excellence (NICE), the Agency for Healthcare Research and Quality (AHRQ), and the German Institute for Quality and Efficiency in Health Care (IQWIG) for new reports and guidelines.

Results

The search update for systematic reviews and meta-analyses resulted in 516 records. Most of them were network analyses. Although the Food and Drug administration (FDA) and the European Medicines Agency (EMA) changed licensing regulations toward cardiovascular outcome trials for glucose-lowering drugs in 2008, reviews mainly focused on surrogate endpoints, such as HbA1c-level. We identified one systematic review on the efficacy of metformin compared to no intervention, placebo, or lifestyle intervention [22], a meta-analysis comparing metformin and SU as monotherapy [23], a systematic review and meta-analysis to assess the effectiveness and safety of the addition of metformin to standard insulin therapy in children with type 1 diabetes aged 6–19 years [24], and an umbrella review of systematic reviews with meta-analysis to assess the efficacy and safety of metformin [25]. Regarding sulfonylureas, we identified two randomized clinical trials comparing glimepiride with dipeptidyl peptidase -IV inhibitors (DPP-IVi): a multicenter, randomized controlled trial to compare the efficacy and safety of glimepiride with saxagliptin in patients with type 2 diabetes inadequately controlled with metformin [26] and a randomized controlled trial comparing the effect of treatment of glimepiride versus linagliptin on cardiovascular safety in patients with type 2 diabetes [27]. With respect to sodium-glucose co-transporter-2 inhibitors (SGLT2i), we identified a randomized controlled trial comparing the efficacy and safety of empagliflozin in patients with type 2 diabetes inadequately controlled on metformin [28] and a randomized controlled trial comparing the efficacy and safety of glimepiride versus ertugliflozin in patients with type 2 diabetes inadequately controlled with metformin [29]. Four trials evaluated the effects of TZDs [30–33]. Systematic reviews about the effectiveness and safety of alpha-glucosidase inhibitors and meglitinides could not be identified. Regarding overall comparisons, a systematic review assessed the efficacy of eight classes of diabetes medications including metformin, sulfonylureas, and alpha-glucosidase inhibitors [34]; two meta-analyses by the Agency for

Healthcare Research and Quality (AHRQ) evaluating all available glucose lowering drugs [35, 36]; a meta-analysis involving 301 clinical trials to assess the efficacy and safety of all classes of oral and injectable antidiabetics, including insulin [37]; and a systematic review including 453 trials comparing the efficacy and safety of nine classes of antidiabetics including monotherapies, add-on to metformin-based therapies and monotherapies versus add-on to metformin therapies [38]. This report includes RCTs and observational studies on (1) comparisons of monotherapies (metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists), (2) comparisons of metformin alone and metformin-based combinations, and (3) comparisons of metformin-based combinations where the second drug was one of the monotherapies or insulin treatment. The evidence was graded separately for both study types. The AHRQ search update was performed through December 2016. Our search for more recent RCTs from January 2016 to November 2021 yielded 310 records.

Metformin

Metformin belongs to the class of biguanides. It is the only still licensed compound of its class after phenformin was withdrawn from the markets. In the University Group Diabetes Program (UGDP) [39, 40], the first large RCT that evaluated the efficacy of glucose lowering drugs on macro- and microvascular outcomes, phenformin, was associated with an increase of cardiac mortality. In contrast, metformin is internationally recommended as initial drug treatment for people with type 2 diabetes [1, 9, 17, 29, 30]. This is mainly based on the results of the UK Prospective Diabetes Study (UKPDS), published in 1998 [41]. About 4000 patients with newly diagnosed type 2 diabetes were enrolled in this RCT. The study objective was to assess the efficacy of intensive blood glucose-lowering therapy compared to conventional treatment (primarily with diet). Patients in the intensive treatment group were supposed to achieve a fasting plasma glucose level of less than 6 mmol/L. The fasting plasma glucose target of the conventional treatment arm was less than 15 mmol/L with no symptoms of hyperglycemia. Non-overweight patients were randomly assigned to intensive treatment with insulin, intensive treatment with sulfonylureas, or conventional therapy with diet. A subgroup of overweight patients had the additional possibility to be randomized to intensive treatment with metformin [41, 42]. A total of 342 patients were assigned to metformin and 411 patients to conventional control with diet [43].

The median HbA1c-level of the intensive treatment group with metformin was 7.4% during the 10 years of follow-up. The conventional group had a median HbA1c-level of 8.0%. Compared to conventional treatment, patients in the metformin monotherapy arm showed significant reductions in *any diabetes-related endpoint*, a composite endpoint comprising the following outcome measures: sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation of at least one digit, vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction. Moreover, *diabetes-related death*, *all-cause mortality*, and *myocardial infarction* significantly decreased in the intensive treatment group with metformin.

Based on these results, metformin became the first-line drug for patients with type 2 diabetes who do not achieve their HbA1c target with diet and other lifestyle interventions alone. However, the results of the UKPDS have not yet been reproduced [2, 44]. The UKPDS was a study with an open-label design, which may lead to overestimated results. The protocol was changed during the study. The initially defined significance threshold of 1% was later changed to 5%. The significant difference in reduction of total mortality and myocardial infarction in the metformin group was above the threshold of 1% [44].

Antihypertensive treatment or statins may have a greater effect on mortality than metformin [45]. This may also explain the results of the UKPDS follow-up study [46], which reported significant reductions in total mortality and cardiovascular mortality for all intensive treatment groups 10 years after the main publication of the UKPDS results. Considering the high risks of bias of the UKPDS, the interpretation of the follow-up results as long-term effect of intensive early glucose control might be misleading [47]. In addition, only about one third of the initially randomized patients were analyzed in the follow-up study.

A meta-analysis that included 13 studies comparing metformin as monotherapy or add-on therapy to diet, placebo, or no treatment found no significant effects on all-cause mortality, cardiovascular mortality, or microvascular complications [48]. Of the included RCTs that assessed patient-relevant outcomes as the primary endpoint [41, 49–51], only UKPDS [41] showed a beneficial effect for treatment with metformin.

In the UKPDS, metformin monotherapy was also associated with a decrease in *any diabetes-related endpoint* and *all-cause mortality* compared to intensive treatment with sulfonylurea or insulin [41]. Data on metformin compared to SU alone were not reported in the UKPDS [23].

The study on the Prognosis and Effect of Antidiabetic Drugs on Type 2 Diabetes Mellitus With Coronary Artery Disease (SPREAD-DIMCAD) [52] compared metformin with the SU glipizide in 304 Chinese people with type 2 diabetes mellitus and coronary artery disease. The targeted HbA1c-level was less than 7% for both groups. The primary endpoint was *recurrent cardiovascular events*, a composite outcome measure comprising nonfatal myocardial infarc-

tion, nonfatal stroke, arterial revascularization, cardiovascular death, and all-cause mortality. The study results showed a significant reduction in this endpoint in favor of the metformin group. However, there is a substantial risk of bias that limits the validity of the study results. The study was retrospectively registered, and there is no study protocol published. Data from 5 years of follow-up were analyzed, but the study drug was only administered for 3 years. It was not reported whether the study treatment was maintained after this time.

A meta-analysis on the effects of SU monotherapy compared to metformin monotherapy did not find any differences between treatment groups regarding all-cause or cardiovascular mortality [23]. A potential benefit of SU over metformin was identified in nonfatal macrovascular outcomes, but definitions of that composite endpoint were heterogeneous. There were no data on microvascular outcomes for a meta-analysis. Results of that meta-analysis were mainly based on "A Diabetes Outcome Progression Trial" (ADOPT), a multicenter, randomized controlled, double-blind trial with 4 years of follow-up [53]. Patients with untreated diabetes were randomized to metformin, glibenclamide, or rosiglitazone. The primary endpoint was *time to treatment failure*, defined as fasting plasma glucose level of more than 180 mg per deciliter after 6 weeks at maximum tolerated dose of the study drug. As this is not a clinical hard endpoint, we excluded this trial from our overview. However, there was no difference regarding all-cause mortality or fatal myocardial infarction between the glibenclamide and metformin groups [23, 53].

Compared to sulfonylureas alone, the combination of metformin and sulfonylureas significantly increased *death from any cause* and *diabetes-related death* in overweight and non-overweight patients in the UKPDS [41]. The meta-analysis by Boussageon et al. [48] confirmed a significant increase in all-cause and cardiovascular mortality for metformin plus SU compared to metformin monotherapy. The results were mainly based on the UKPDS. After excluding this study, no group difference was seen in both endpoints.

The Hyperinsulinemia: The Outcome of Its Metabolic Effects (HOME) trial evaluated the efficacy of metformin in the Netherlands [51]. The RCT included 390 overweight and obese patients with type 2 diabetes. Metformin added to insulin therapy was compared to insulin monotherapy. After about 4 years, there was no difference between groups regarding cardiovascular and total mortality or microvascular outcomes (progression of retinopathy, nephropathy, and neuropathy) but a significant reduction in a combined macrovascular endpoint for patients with metformin plus insulin treatment. This composite endpoint included a total of 13 separate outcome measures, for example, myocardial infarction, heart failure, stroke, diabetic foot, percutaneous transluminal coronary angioplasty, nontraumatic amputation, and sudden death. Patients' characteristics were unequally distributed between the study groups at baseline. For example, in the metformin group, there were fewer smokers (19% vs. 30%) and more patients with antihypertensive medication (47% vs. 39%). In addition, the number of non-completers differed between the metformin plus insulin study arm ($n = 65$) and the insulin alone arm ($n = 48$), mainly because of adverse events.

A systematic review that analyzed RCTs published until February 2017 [22] found similar results regarding the efficacy of metformin. The authors identified no more recent RCTs than earlier meta-analyses, but study selection was not completely transparent. The UKPDS [41] was included in the meta-analysis, but only the combination of metformin and SU compared to SU alone, not the comparison of metformin with diet or metformin monotherapy with SU. Moreover, the authors included the 10 years follow-up UKPDS in their analysis, and observational studies were excluded. In fact, the level of evidence of the UKPDS follow-up publication [46] is quite similar to observational studies due to the already mentioned risks of bias [44, 47].

Compared with other interventions, metformin does not increase the risk of mild or severe hypoglycemia. The main adverse events associated with metformin are gastrointestinal, especially diarrhea. There have been warnings of lactic acidosis due to metformin. A Cochrane review [54] and the AHRQ report [36] did not find an increased risk of lactic acidosis with the use of metformin. Up to 2016, metformin was not recommended for patients with moderate to severe kidney function. Following this advice to practicing physicians might be one reason for a low number of reported cases of lactic acidosis. In 2016, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) changed their recommendations to allow the use of metformin in patients with moderately reduced kidney function (GFR = 30–59 mL/min) [55, 56]. The FDA explicitly recommends assessment of risks and benefits in patients with metformin whose GFR fall below 45 mL/min/1.73 m^2. Starting metformin in patients with eGFR between 30–45 mL/min/1.73 m^2 was not recommended [56].

Sulfonylureas

The first-generation SU tolbutamide and chlorpropamide were introduced in the 1950s. In the UGDP, tolbutamide increased mortality risk. Nonetheless, both substances were extensively used even after publication of the UGDP in many countries. Today, first-generation SU have been replaced by the second- and third-generation SU. SU are recommended as initial drug therapy if metformin is contraindicated or not tolerated by patients [1, 17, 18]. The com-

parative effects of SU to metformin are already described in the metformin part of this chapter. We additionally searched for systematic reviews and RCTs on the efficacy of SU as monotherapy compared to diet, placebo, or lifestyle interventions.

As in our original overview [2], the only RCT that met our inclusion criteria was the UKPDS [42]. In the UKPDS 33, the effects of intensive blood-glucose control with either SU or insulin were compared to conventional treatment. A total of 615 patients were assigned to glibenclamide, and 896 received conventional treatment, which comprised dietary advice. Over 10 years, median HbA1c values were 7.2% for glibenclamide and 7.9% for conventional therapy. More patients in the conventional treatment arm had reached the primary endpoint *"any diabetes-related endpoint"* and microvascular complications, but there were no significant effects on macrovascular outcomes. The effect on the microvascular outcome was mainly attributed to fewer cases of retinal photocoagulation [42]. Patients in the SU group gained more weight (1.7 kg) than patients in the conventional treatment group, and more patients receiving SU had major hypoglycemic events (1.4% vs. 0.7%) over 10 years (Table 34.2).

Thiazolidinediones

Thiazolidinediones were introduced in the 1990s. The first agent of this class, troglitazone, was withdrawn from the market because of the increased risk of severe liver damage and toxicity. The remaining compounds, rosiglitazone and pioglitazone, were under selling restrictions or withdrawn in some countries due to safety issues. Meta-analyses showed an increased risk of myocardial infarction in patients who received rosiglitazone [57, 58]. One of the included studies was the RECORD trial with a mean follow-up of 5.5 years [59]. A total of 4447 patients who were treated with metformin or SU monotherapy were randomized to additional rosiglitazone or additional metformin/SU. Patients of the rosiglitazone group had a twofold greater risk of fatal and nonfatal heart failure compared to patients with metformin plus SU treatment. There was no difference between groups regarding the combined primary endpoint, *cardiovascular death or cardiovascular hospitalization*. Patients receiving rosiglitazone therapy reported significantly more bone fractures. Further adverse effects of rosiglitazone comprised weight gain and edema [59]. Findings from the ADOPT trial confirmed higher cardiovascular risks and other adverse effects associated with rosiglitazone [53].

Table 34.2 Metformin and sulfonylurea, identified evidence on efficacy of single RCTs

Comparison	Outcome	Events in groups (%)	Effect RR [95% CI]	ARR [95% CI]	Participants	Study/risk of bias
Intensified therapy with metformin vs. conventional therapy with diet	Any diabetes-related endpoint	98 (28.7) vs. 160 (38.9)	0.68 [0.58, 0.87]	10.3 [3.55, 17.0][a]	Overweight and obese patients with newly diagnosed T2DM Metformin $n = 342$ diet $n = 411$ Follow-up: 10.7 years	UKPDS 34 (1998) [41]: Open-label design, change of protocol and primary endpoint during study, insufficient blinding, limited information on accompanying treatment during the study
	Diabetes-related death	28 (8.2) vs. 55 (13.4)	0.58 [0.37, 0.91]	5.2 [0.8, 9.59][a]		
	All-cause mortality	50 (14.6) vs. 89 (21.7)	RR 0.64 [0.45, 0.91]	7.0 [1.57, 12.5][a]		
	Myocardial infarction	39 (11.4) vs. 73 (17.8)	RR 0.61 [0.41, 0.89]	6.4 [1.36, 11.36][a]		
	Stroke		n.s.			
	Peripheral vascular disease		n.s.			
	Microvascular disease		n.s.			
Intensified therapy with glyburide (SU) vs. conventional therapy with diet	Any diabetes-related endpoint	221 (35.9) vs. 376 (42.0)	0.82 [0.69, 0.97]	6.0 [1.04, 11.01][a]	Patients with newly diagnosed T2DM, BMI ~ 27.5 Glyburide $n = 615$ Diet $n = 896$ Follow-up: 11.1 years	UKPDS 33 (1998) [42]: High risk of bias (see above)
	All-cause mortality		n.s.			
	Myocardial infarction		n.s.			
	Stroke		n.s.			
	Microvascular complications	49 (8.0) vs. 104 (11.6)	0.66 [0.47, 0.93]	3.6 [0.64, 6.64][a]		

(continued)

Table 34.2 (continued)

Comparison	Outcome	Events in groups (%)	Effect RR [95% CI]	ARR [95% CI]	Participants	Study/risk of bias
Intensive therapy with metformin vs. intensive control using chlorpropamide, glyburide, or insulin	Any diabetes-related endpoint	98 (28.7) vs. 350 (36.8)	0.78 [0.65, 0.94][a]	8.1 [2.46, 13.84][a]	Overweight and obese patients with newly diagnosed T2DM Metformin n = 342 intensive control n = 951 Follow-up: 10.7 years	UKPDS 34 (1998) [42]: High risk of bias (see above)
	Diabetes-related death		n.s.			
	All-cause mortality	50 (14.6) vs. 190 (20.0)	0.73 [0.55, 0.97][a]	5.4 [0.83, 9.89][a]		
	Myocardial infarction		n.s.			
	Stroke		n.s.			
	Peripheral vascular disease		n.s.			
	Microvascular disease		n.s.			
Intensive therapy with metformin + sulfonylurea vs. intensive therapy with sulfonylurea alone	Any diabetes-related endpoint		n.s.		Non-overweight and overweight patients with newly diagnosed T2DM Met+SU n = 268 SU n = 269 Follow-up: 10.7 years	UKPDS 34 (1998) [42]: High risk of bias (see above)
	Diabetes-related death	28 (10.4) vs. 14 (5.2)	RR 1.96 [1.02, 3.75]	−5.2 [−9.77, −0.72][a]		
	All-cause mortality	47 (17.5) vs. 31 (11.5)	RR 1.60 [1.02, 2.52]	−6.0 [−11.95, −0.07][a]		
	Myocardial infarction		n.s.			
	Stroke		n.s.			
	Peripheral vascular disease		n.s.			
	Microvascular disease		n.s.			
Metformin vs. glipizide (SU)	Composite cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, arterial revascularization, cardiovascular death, and all-cause mortality)	43 (27.6) vs. 60 (40.5)	Adjusted HR 0.54 [0.30, 0.90] (adjusted for duration of diabetes, duration of CAD, age, sex, smoking)	13.0 [2.41, 23.55][a]	RCT Patients with T2DM and CAD Metformin n = 156 glipizide n = 148 Follow-up: 5 years Treatment target: HbA1c <7.0%	Hong et al. 2013 [52]: Small sample size, intervention finished after 3 years, but outcome assessment after 5 years
	Hypoglycemia		n.s.			
Metformin + insulin vs. placebo + insulin	All-cause mortality		n.s.		Patients with T2DM Metformin n = 196 placebo n = 194 Follow-up: 4.3 years Treatment target: FPG 4-7 mmol/L, postprandial 4–10 mmol/L	Kooy et al. 2009 [51]: Unequal baseline characteristics between groups, low power, non-completers differed between groups
	Cardiovascular death		n.s.			
	Microvascular outcome		n.s.			
	Macrovascular outcome	(15%) vs. (18%)	Adjusted HR 0.60 [0.40, 0.92] (adjusted for age, sex, smoking, cardiovascular history)	−6.1 [−10.5, −1.5]		
	Macro- and microvascular outcomes		n.s.			
	Hypoglycemia		n.s.			

Table adapted from [3]. *T2DM* type 2 diabetes mellitus, *n.s.* not significant, *RR* risk ratio, *HR* hazard ratio, *ARR* absolute risk reduction, *CAD* coronary artery disease

[a]Calculated with data from the original study publication

The FDA restricted access to rosiglitazone, which was part of the Risk Evaluation and Mitigation Strategy (REMS), and the RECORD trial showed several risks of bias. The RECORD trial was an open-label trial with low statistical power. An unplanned interim analysis was conducted, which could have repealed blinding. Patients' compliance to rosiglitazone was low. In December 2015, based on an independent review of the study, the FDA stated that REMS was no longer needed and that the benefits of rosiglitazone outweighed the risks. In their Standards of Medical Care in Diabetes, the American Diabetes Association recommended TZD as add-on therapy or monotherapy if metformin was contraindicated [58].

In our updated search, we identified a meta-analysis on the effect of pioglitazone on cardiovascular outcomes, which also included participants with pre-diabetes and insulin resistance [32]. The primary endpoint was major adverse cardiovascular events (MACE) comprising cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The use of pioglitazone in patients with diabetes was associated with lower risks of MACE, and the incidence of myocardial infarction or stroke did not differ between the pioglitazone and control groups. Pioglitazone was also associated with an increased risk of heart failure, bone fracture, edema, weight gain, and hypoglycemia [32]. The largest included RCT was the PROactive trial [60]. Patients with type 2 diabetes and previous stroke were randomized to receive pioglitazone or placebo, and the mean study duration of the study was 34.5 months. Albeit there was a reduction in the combined endpoint, *death from any cause, nonfatal MI,* and *stroke* for patients randomized to receive pioglitazone, patients in this group had significantly higher risks of heart failure, edema, and weight gain in addition to a nonsignificant higher rate of bladder cancer [60]. In the meta-analysis, no significant differences were found in bladder or any cancer risk [32]. Another meta-analysis reported a significantly higher risk [31], but it was mainly based on the results of the PROactive trial. A systematic review on the effects of TZD on bone fractures confirmed an increased risk of fractures in women who use rosiglitazone or pioglitazone [30]. The National Institute for Clinical Excellence (NICE) recommends pioglitazone when metformin is contraindicated but explicitly points out the risks of adverse events (Table 34.3) [18].

Table 34.3 Thiazolidinedione, identified evidence from RCTs

Comparison	Outcome	Events in groups (%)	Effect RR [95% CI]	ARR [95% CI]	Participants	Study/risk of bias
Rosiglitazone + metformin or SU vs. metformin + SU	Primary endpoint (CV death or CV hospitalization)		n.s.		Overweight and obese patients with T2DM Rosiglitazone $n = 2220$ Met+SU $n = 2227$ Follow-up: Mean 5.5 years Treatment target: HbA1c ≤ 7.0%	RECORD (2009) [59]: Misleading primary endpoint, high non-compliance, low statistical power, unplanned interim analysis
	All-cause mortality		n.s.			
	Cardiovascular mortality		n.s.			
	Myocardial infarction		n.s.			
	Stroke		n.s.			
	Fatal and nonfatal heart failure	61/2220 vs. 29/2227	2.11 [1.36, 3.27][a]	−1.4 [−2–27, −0.62][a]		
	Fractures	185/2220 vs. 118/2227	1.57 [1.26, 1.97]	−3.0 [−4.51, −1.57][a]		
Pioglitazone + other glucose-lowering drugs vs. placebo + other glucose-lowering drugs	Primary endpoint (all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, coronary or leg arterial revascularization, amputation above ankle)		n.s.		Obese patients with T2DM and high CV-risk Pioglitazone $n = 2605$ Placebo $n = 2633$ Follow-up: 2.9 years Treatment target: HbA1c <6.5%	PROactive (2005) [60]: Misleading interpretation of data, definition of secondary endpoint afterwards
	Main secondary endpoint (death from any cause, nonfatal MI, stroke)	301 (11.6) vs. 358 (13.6)	0.85 [0.74, 0.98][a]	2.0 [0.25, 3.84][a]		
	Death		n.s.			
	Heart failure	281 (10.8) vs. 198 (7.5)	RR 1.43 [1.21, 1.71][a]	−3.3 [−4.83, −1.71][a]		
	Edema without heart failure	562 (21.6) vs. 341 (13.0)	RR 1.67 [1.47, 1.88][a]	−8.6 [−10.66, −6.59][a]		

Table adapted from [3]. *T2DM* type 2 diabetes mellitus, *n.s.* not significant, *RR* relative risk, *ARR* absolute risk reduction, *MI* myocardial infarction, *CV* cardiovascular

[a]Calculated with data from original study publication

Alpha Glucosidase Inhibitors and Meglitinides

The ADA and the EASD do not explicitly recommend the use of AGIs due to their modest effects, but they accept that AGIs *"may be tried in specific situations"* [9]. Two Cochrane reviews including patients with type 2 diabetes and patients with impaired glucose tolerance did not find significant effects of AGIs on mortality or morbidity [61, 62]. We did not include the STOP-NIDDM trial in this overview because of its high risk of bias, which was extensively discussed in the literature. The Acarbose Cardiovascular Evaluation Trial (ACE) [63] evaluated the efficacy of acarbose on cardiovascular death, nonfatal MI, and nonfatal stroke in patients with impaired glucose tolerance and coronary heart disease. This RCT was completed in April 2017, and the results showed that patients received acarbose achieved a statistically significant reduction on 18% in the relative risk of diabetes, without reduction in the risk of major adverse cardiovascular events (MACE).

Meglitinides same as SU belong to the drug class of insulin secretagogues. Compounds of this class are nateglinide and repaglinide. In contrast to SU, they are rapid-acting secretagogues. The ADA and the EASD stated that meglitinides may be used as an alternative to SU in patients with irregular meal schedules [10]. In case repaglinide is considered as alternative to metformin, the NICE guidance on *Type 2 diabetes in adults* suggests physicians to inform patients that there is no licensed non-metformin-based combination with repaglinide [15]. There is no evidence on effects regarding clinically relevant and long-term outcomes with the use of meglitinides [64].

Conclusion

In conclusion, the older classes of oral antidiabetic agents still play central roles in diabetes care, but evidence on macro- and microvascular risk is lacking or insufficient.

The applicability of the results of clinical trials is limited due to the short duration of the studies [35]. Most studies assess the efficacy of medications on intermediate outcomes rather than long-term hard clinical endpoints [34, 35, 38]. Intermediate outcomes or surrogates must be interpreted with caution. Medications decreasing HbA1c-values do not necessarily reduce morbidity or mortality. In some cases of withdrawn drugs, blood glucose levels decreased, while risks of hard clinical endpoints did not change or even increased. Whenever RCTs included patient-relevant endpoints, they were mostly assessed as secondary endpoints or adverse effects. Available studies were often too small to identify any differences between groups. Composite outcome measures, such as *any diabetes-related endpoint* or *macrovascular complications*, which usually comprise endpoints of varying importance and validity, are challenging to interpret and may lead to overinterpretation of single outcomes.

The authors of the AHRQ report [36] concluded that the efficacy of all diabetes medications regarding all-cause mortality, cardiovascular and cerebrovascular morbidity as well as retinopathy, nephropathy, and neuropathy is still uncertain. The report showed moderate strength of evidence that sulfonylurea monotherapy compared with metformin alone was associated with an increased risk of cardiovascular mortality. This result was mainly based on two RCTs: ADOPT with patients with newly diagnosed diabetes and SPREAD-DIMCAD, which included patients with coronary heart disease. In contrast, the meta-analysis by Madsen et al. [23] did not find any differences between SU and metformin monotherapy of total or cardiovascular mortality but a potential benefit of SU regarding nonfatal macrovascular outcomes. However, definition of the composite endpoint differed between studies [23].

In the AHRQ report [36], evidence on intermediate outcomes, such as HbA1c values, was graded as high, and effects on HbA1c values were comparable between most oral antidiabetic agents. Monotherapy comparisons of metformin with sulfonylurea and metformin with TZDs show similar effects with respect to reduction in HbA1c values [65]. Moreover, metformin monotherapy reduced body weight more than TZDs or SU, though the clinical relevance of these differences may be debatable. Metformin monotherapy shows greater weight reduction when compared with the combination of metformin and SU or metformin plus TZDs, respectively [36, 66]. In addition, metformin was favored over SU monotherapy, the combination of metformin and TZDs, and over the combination of metformin and SU regarding hypoglycemia [67]. The risk of hypoglycemia is higher for SU than for TZDs [36], albeit differences in the risk of hypoglycemia have been documented, probably explained by differences in chemical structure, pharmacogenetic and pharmacodynamic properties between sulfonylureas [68].

Despite there is only one RCT with a small sample size, which demonstrated an effect on hard clinical endpoints, metformin is internationally recommended as first-line drug for patients with type 2 diabetes. It is used as comparator for the evaluation of new medications although high-quality evidence on patient-relevant outcomes is missing. Thus, the role of metformin as "gold standard" is questionable. Despite a huge number of studies and a stunning total of 427 meta-analysis until 2021, evidence on metformin in observational studies generally does not seem reliable, due to substantial heterogeneity between studies, small-study effects, and excess significance, while evidence from randomized trials suggests only a few effects with strong evidence for additional benefits [25].

Shared Decision-Making

Even though there is no single perfect treatment of hyperglycemia in patients with type 2 diabetes, decisions about treatment policies and diabetes drug therapy are made for thousands of patients every day. For many decades, the dominant approach to making decisions about treatment in the medical encounter has been one of paternalism, but in recent years, this model has been challenged by doctors, patients, medical ethicists, and researchers who advocate more of a partnership relation between doctors and patients [69]. Shared decision-making is a personalized and patient-centered approach [70] described by Charles, Gafni, and Whelan in 1997 to help patients and clinicians to select the treatment that best fits individual patient needs, values, and preferences [71]. It is a special way of conversation between patients and healthcare professionals comprising various elements, such as clarifying the patient's situation, noticing that there is more than one treatment option, information about benefits and harms of the treatment options, and weighing up the pros and cons considering patient values and expectations. Patient decision aids are tools to promote SDM. They are proved to improve patients' knowledge about treatment options and about probabilities of benefits and adverse effects of each option. Moreover, they help patients to find the option that is most important to them [16]. Decision aids can be used to prepare patients for the consultation with their clinician or within consultations [15]. We have developed an evidence-based patient decision aid on the prevention of myocardial infarction and a corresponding group counselling session in which diabetes educators help patients to understand the information and to define and prioritize own treatment goals regarding statin uptake, smoking cessation, and HbA1c and blood pressure goals [19, 20]. The intervention (informed shared decision-making program; ISDM) was evaluated in a proof of concept RCT [19]. Patients of the ISDM group achieved higher levels of risk comprehension and realistic expectations about benefits and harms of treatment options. For the following cluster RCT with family practices, we added a structured SDM training for physicians and a patient-held documentation sheet to the intervention in order to optimize the consultation in terms of SDM [72]. The study results showed that the whole ISDM program could be successfully implemented in everyday practice. Patients and clinicians of the ISDM group pursued common treatment goals significantly more frequently than the control group [73].

Figure 34.1 displays a 100-stick figure pictogram and bar graphs to visualize probable effects of more or less intensified glucose control on the combined diabetes-related endpoint (UKPDS 34) as used in our patient decision aid and group teaching session [19, 20, 72].

Effects on *"any diabetes related event"* can be explained as follows:

The term "any diabetes related event" is a collective term for different complications of diabetes. It included death from hyperglycemia (high blood sugar) or hypoglycemia, heart attack, angina, heart failure, stroke, kidney failure, amputation, vitreous hemorrhage in the eye (bleeding from abnormal blood vessels in the eye, which can lead to blindness), damage to the retina, blindness of one or both eyes, or eye surgery for cataract.

In the following, you can see the results from the UKPDS [41]. This is a study that was performed in Great Britain and lasted 10 years.

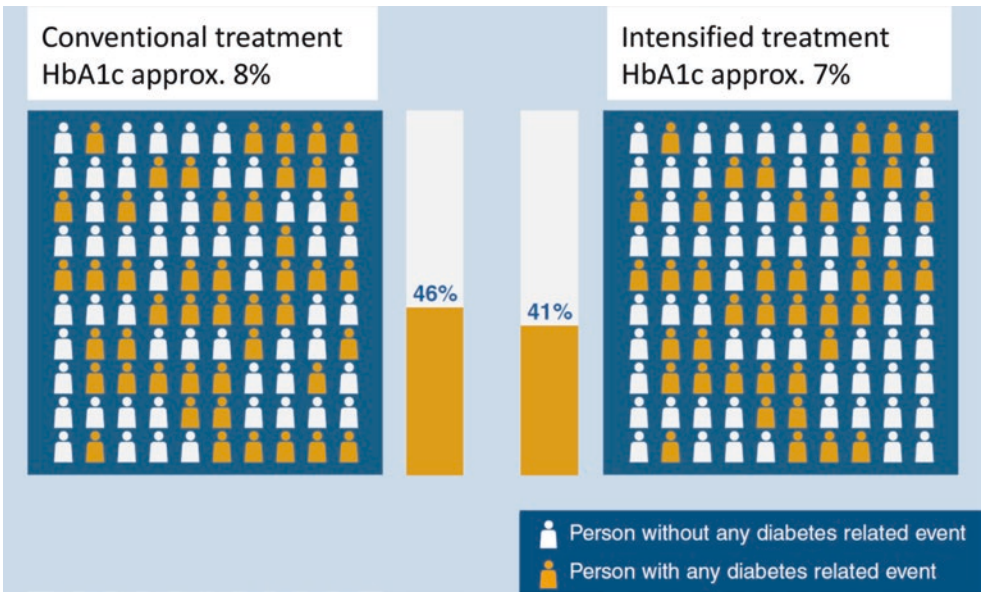

Fig. 34.1 Blood sugar control and "any diabetes-related event"

Imagine two groups, each with 100 patients with type 2 diabetes followed for 10 years.

One group was treated intensively with medication to control blood sugar levels. Patients of that group achieved an average HbA1c of 7%.

The comparator (control group) was treated conventionally with less intensive medication and achieved an average HbA1c of 8%.

- In the group with conventional treatment, "any diabetes-related event" occurred in 46 of the 100 patients during the 10 years period.
- In the group with intensive control, "any diabetes-related event" occurred in 41 of the 100 patients during the 10 years period.

That means, intensive blood sugar control over 10 years prevented "any diabetes-related event" in *5 of 100 patients*. The remaining 95 of 100 people had no benefit from the intensive treatment over a period of 10 years because they also experienced a diabetes-related event (41 patients) or because they would not have experienced any event even with conventional treatment (54 patients).

Intensively treated patients also experienced harm due to hypoglycemia. An additional 7 out of 100 people suffered severe hypoglycemia with intensive treatment compared to the comparator group over 10 years [41].

Communication of uncertainties is challenging. No one can say if one particular patient would benefit from intensive treatment. Presenting the data helps patients to weigh up the pros and cons making a decision, which meets personal preferences and values. Moreover, the effects of antihypertensive treatment and statin intake should be taken into consideration. For example, intensive blood pressure lowering over 8 years (achieved RR 145/82 mmHg) prevented "any diabetes-related event" in 16 out of 100 patients [74].

According to ADA and EASD recommendations [9, 10], clinicians should talk with patients about the pros and cons of medications to achieve individual treatment goals. In our ISDM program, diabetes educators explain benefits and harms of evidence-based options to prevent cardiovascular complications. They guide patients to estimate their individual heart attack risk and then calculate their risks with and without statin intake and to estimate comparable effects of hypertensions or blood glucose control [19, 72].

Since efficacy of single diabetes medications seems uncertain [36], information about antidiabetic agents can only focus on intermediate outcomes, such as weight change, HbA1c values, hypoglycemia, and other side effects. Montori's research group developed and evaluated diabetes medication choice decision aid cards on intermediate effects to be used during the clinical encounter [75]. Patients had improved knowledge and were more involved in the decision-making process [75]. Another decision aid addressed statin choice to prevent myocardial infarction in patients with type 2 diabetes [76, 77]. There are also interactive and web-based decision aids that are supposed to foster shared decision-making and goal setting [78] and patient decision aids on special treatments, such as starting insulin [79].

Communication of quality of data is challenging. Patient decision aids are supposed to provide the best available evidence. However, sometimes, there is no good evidence, but patients have the right to know. Information on level of evidence is provided in guidelines and should be included in the patient information material.

Diabetes care is complex and has to be individualized. The level of evidence of antidiabetic agents on patient-relevant outcomes is low, and it has been shown that treatment of hypertension is more effective than treatment of blood glucose [42]. New therapeutic classes have enlarged the scope of antidiabetics, and their cardiovascular and renal benefits are advantageous by comparison with the "old antidiabetics" [80]. Beyond these achievements, the first antidiabetics continue to be part of the clinical armamentarium because of efficacy and costs. Last but also very important, involving patients in decision-making and making informed choices should be standard in the medical encounter.

Multiple Choice Questions

1. Which is the aim of the treatment of type 2 diabetes?
   (a) Fasting blood glucose control
   (b) Avoid acute symptoms of hyperglycemia and prevent macro- and microvascular complications
   (c) Post-prandial blood glucose control
   (d) Increase the use of medications
   (e) Weight reduction and control
2. Rigid treatment regimes with low HbA1c targets:
   (a) Have resulted in better patient-relevant outcomes
   (b) Have produced equal patient-relevant outcomes
   (c) Are associated with higher risks of mortality
   (d) Improve health-related quality of life
   (e) Reduce hospital admissions and costs
3. What was the argument to withdraw several new antidiabetic agents from the German market?
   (a) No additional benefit over usual care could be demonstrated and health insurances would not have covered additional costs
   (b) Higher costs compared with traditional medications
   (c) Higher risk of hypoglycemia
   (d) Unacceptable risk of nondiabetic ketoacidosis
   (e) All of the above
4. According to the recent ADA and EASD recommendations, clinicians should not discuss with patients the pros and cons of medications to achieve individual treatment goals.

(a) False
(b) True

5. What is the mechanism of action of metformin?
   (a) Reduction of insulin resistance in target cells through transcription of several genes involved in glucose and lipid metabolism
   (b) Inhibition of alpha-glucosidase, delaying intestinal degradation of complex carbohydrates and prolonging post-prandial glucose absorption.
   (c) Multiple sites of action, including increase of insulin sensitivity by increasing peripheral glucose uptake, decrease of intestinal glucose absorption, and decrease of hepatic glucose production
   (d) Stimulation of insulin release in pancreatic beta cells. Decrease in hepatic clearance of insulin. Additional extra-pancreatic mechanisms
   (e) Increase insulin sensitivity by skeletal muscle
6. What is the mechanism of action of glyburide?
   (a) Reduction of insulin resistance in target cells through transcription of several genes involved in glucose and lipid metabolism
   (b) Inhibition of alpha-glucosidase, delaying intestinal degradation of complex carbohydrates and prolonging post-prandial glucose absorption
   (c) Increase of insulin sensitivity by increasing peripheral glucose uptake, decrease of intestinal glucose absorption, and decrease of hepatic glucose production
   (d) Stimulation of insulin release in pancreatic beta cells. Decrease in hepatic clearance of insulin. Additional extra-pancreatic mechanisms.
   (e) Increase insulin sensitivity by skeletal muscle
7. What is the mechanism of action of thiazolidinediones?
   (a) Reduction of insulin resistance in target cells through transcription of several genes involved in glucose and lipid metabolism
   (b) Inhibition of alpha-glucosidase, delaying intestinal degradation of complex carbohydrates and prolonging post-prandial glucose absorption
   (c) Increase of insulin sensitivity by increasing peripheral glucose uptake, decrease of intestinal glucose absorption, and decrease of hepatic glucose production
   (d) Stimulation of insulin release in pancreatic beta cells. Decrease in hepatic clearance of insulin. Additional extra-pancreatic mechanisms.
   (e) Increase insulin sensitivity by skeletal muscle
8. What is the mechanism of action of alpha-glucosidase inhibitors?
   (a) Reduction of insulin resistance in target cells through transcription of several genes involved in glucose and lipid metabolism
   (b) Inhibition of alpha-glucosidase, delaying intestinal degradation of complex carbohydrates and prolonging post-prandial glucose absorption
   (c) Increase of insulin sensitivity by increasing peripheral glucose uptake, decrease of intestinal glucose absorption, and decrease of hepatic glucose production
   (d) Stimulation of insulin release in pancreatic beta cells. Decrease in hepatic clearance of insulin. Additional extra-pancreatic mechanisms
   (e) Increase insulin sensitivity by skeletal muscle
9. The evidence sustaining that sulfonylurea monotherapy compared with metformin alone was associated with an increased risk of cardiovascular mortality comes from:
   (a) Experiences of primary care practitioners
   (b) Two clinical trials: ADOPT with patients with newly diagnosed diabetes and SPREAD DIMCAD, which included patients with coronary heart disease
   (c) Pharmaco-vigilance reports
   (d) Conclusions of consensus groups
   (e) The results of the Diabetes Control and Complications Trial (DCCT)
10. Moderate strength of evidence suggest sulfonylurea monotherapy compared with metformin alone was associated with:
   (a) Higher risk of cardiovascular mortality
   (b) An increase in metabolic control
   (c) Lower weight gain
   (d) Reducing oxidative stress and pro-inflammatory molecules
   (e) Lower risk of severe hypoglycemia

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Incretin Therapies: Current Use and Emerging Possibilities

35

Haiko Schlögl and Michael Stumvoll

Abbreviations

ATP	Adenosine triphosphate
bpm	Beats per minute
cAMP	Cyclic adenosine monophosphate
cAMP-GEF-2	cAMP-guanine nucleotide exchange factor 2
CCK	Cholecystokinin
CI	95% confidence interval
CVOT	Cardiovascular outcome trial
DPP-4	Dipeptidyl-peptidase 4
fMRI	Functional magnetic resonance imaging
GIP	Gastric inhibitory polypeptide (also: glucose-dependent insulinotropic peptide)
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c
HR	Hazard ratio
IgG	Immunoglobulin G
IV	Intravenous
K_{ATP} channel	ATP-sensitive potassium channel
K_V channel	Delayed rectifying potassium channel
LAR	Long acting release
PYY	Peptide YY
SC	Subcutaneous
T1R	Taste receptor type 1
T2D	Type 2 diabetes
USFDA	United States Food and Drug Administration
vs.	Versus

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History of Incretins

Discovery of the Incretin Effect

In the last two decades, analogs of the incretin glucagon-like peptide-1 (GLP-1) became an important pillar of the therapy of type 2 diabetes (T2D). Still, incretins are a fascinating focus of current research. The term "incretin" denotes the entity of hormones that are secreted by the mucosal cells of the intestine and increase the secretion of insulin from the β-cells of the pancreas. The history of studies examining incretin effects goes far. The first comprehensive experiment proving the effects of incretins on the pancreas of animals was reported already as early as in the year 1902 by English physiologists Bayliss and Starling [1]. In this groundbreaking early research, the jejunum of a dog was cut from all nervous connections including those to the pancreas, but the blood vessels between the intestine and the pancreas were kept intact. The introduction of a liquid mimicking chyme into the jejunum resulted in an increase of pancreatic secretion. Authors concluded absolutely correctly that "*since this part of the intestine was completely cut off from nervous connection with the pancreas, the conclusion was inevitable that the effect was produced by some chemical substance finding its way into the veins of the loop of jejunum in question and being carried in the blood-stream to the pancreatic cells*" [1]. Today, we know that incretins belong to the group of these "*chemical substances*," which are secreted after the ingestion of food.

In the 1960s, it could be demonstrated, also in humans, that orally administered glucose induced a greater insulin response than intravenously (IV) administered glucose [2–4]. This effect was then termed the "incretin effect," and in 1971, the first hormone contributing to this effect was isolated: the peptide hormone called gastric inhibitory polypeptide (GIP, later also termed glucose-dependent insulinotropic peptide) was identified in the intestinal mucosa of a dog. Already at this early stage, an important property of the incretins could be demonstrated for GIP: its

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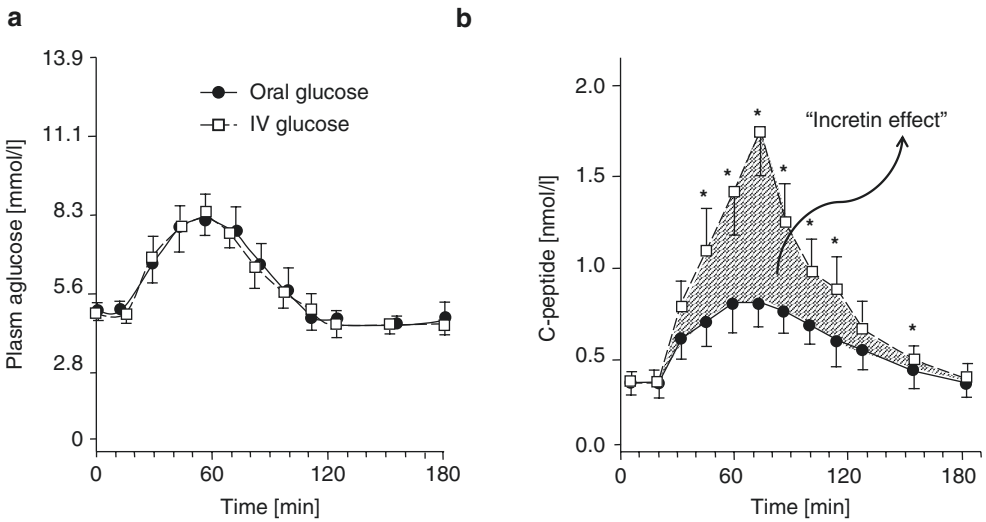

Fig. 35.1 Mean (± standard error of the mean) peripheral venous plasma glucose (**a**) and C-peptide (**b**) concentrations after oral (empty squares) and intravenous (IV, full circles) administration of 50 g glucose in six healthy, normal weight participants aged 28–33 years. *IV* intravenous, * $p < 0.05$ between oral and IV glucose administration. (Modified from [6])

insulinotropic effect is blood glucose dependent. Only if blood glucose is elevated GIP induces insulin secretion [5]. In 1985, a second peptide with the same blood glucose-dependent insulinotropic effects was discovered in rats and later also found in humans and termed glucagon-like peptide-1 (GLP-1). In humans, by comparing insulin secretion of the pancreas after IV glucose administration versus oral glucose administration, it could be demonstrated that in healthy, normal weight adults, incretin action is responsible for at least half of the total insulin secreted [6] (Fig. 35.1). Today, we know that circulating GIP concentrations are tenfold higher than GLP-1 concentrations, but GLP-1 seems to be more potent than GIP.

First Clinical Usage

In 2005, with exenatide, the first drug was approved, which pharmacologically uses the incretin effect. Exenatide is an analog of endogenous GLP-1 and activates the GLP-1 receptor, leading to an increase in insulin secretion of the β-cell if blood glucose is elevated. Shortly after, with sitagliptin, the first member of a second drug class using the incretin effect was approved for the treatment of T2D. Sitagliptin is an inhibitor of the enzyme dipeptidyl-peptidase 4 (DPP-4), which degrades endogenous GLP-1. By blocking the enzyme, the drug increases endogenous GLP-1 concentrations and thus increases the incretin effect.

In this chapter, we will highlight the physiological actions of the incretins GLP-1 and GIP in the human body (with a focus on GLP-1), summarize, and discuss clinical data of drugs using the incretin pathways in the treatment of T2D. Furthermore, we will give an outlook on emerging possibilities of incretin use in diabetes treatment.

Mechanisms of Physiologic Action of Endogenous GLP-1

Stimulation of GLP-1 Secretion

GLP-1 is a 30-amino acid peptide hormone, created by cleavage of the processor peptide proglucagon. The physiologic function of GLP-1 is the mediation of metabolization of ingested nutrients, analog to the function of insulin. Its main sites of secretion are the L-cells of the distal ileum and colon, but GLP-1 is also secreted in other parts of the intestine, in the pancreas, and also in the brain. In the intestine, proglucagon is cleaved into GLP-1 and several other peptides. Production of GLP-1 in the L-cells of the distal ileum and the colon happens as a response to intraluminal nutrients. After meal digestion, intraluminal fats in the distal parts of the ileum bind to fatty acid receptors on the surface of L-cells, leading to GLP-1 secretion. Intestinal sugars are most likely detected by the classic sweet taste receptor of the taste receptor type 1 (T1R)-family, the T1R3. Receptor binding on the surface of the intestinal L-cell leads to GLP-1 secretion. Probably, also the sodium-glucose cotransporter 1 contributes to intraintestinal sugar-mediated GLP-1 release [7]. Furthermore, digested peptides elicit GLP-1 secretion, whereas the molecular mechanisms are not yet fully understood (Fig. 35.2).

Effects on the Pancreas

Endogenous GLP-1 has several important effects involved in the consumption and digestion of food (Table 35.1). The most important GLP-1 effect for the treatment of diabetes is the stimulation of insulin secretion of the β-cells of the pancreas. GLP-1-independent insulin secretion of the β-cell,

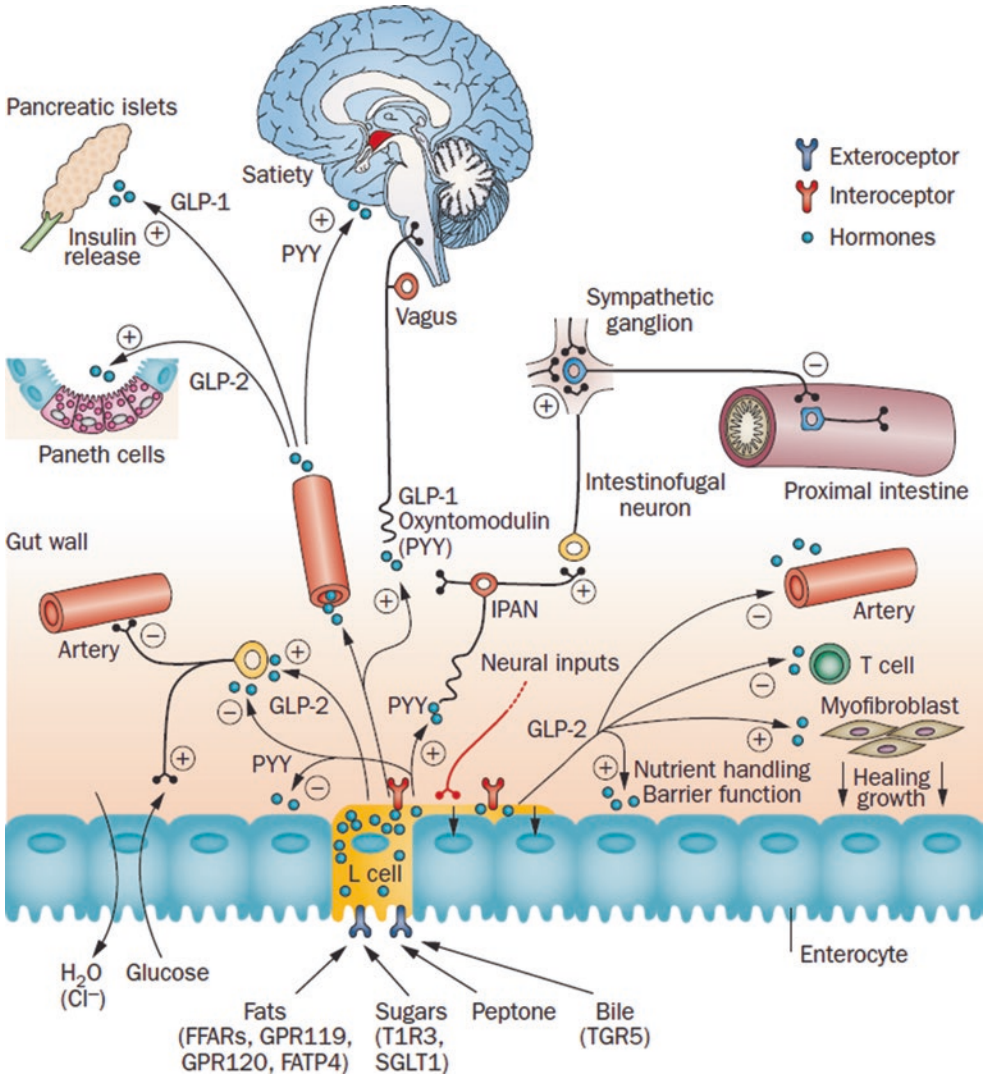

Fig. 35.2 Physiological actions of intraintestinal nutrients (fats, sugars, peptides) and bile on the L-cell of the distal ileum and elicited signal transduction in the regulation of anabolic metabolism. The L-cell expresses exteroceptors for free fatty acids, sugars, protein fragments (peptones) and bile acids. L-cells release the hormones glucagon-like peptide-1 (GLP-1), GLP-2 (another cleavage product of proglucagon, co-secreted with GLP-1, also acting in the intestine, but not yet fully understood), peptide YY and oxyntomodulin. These hormones have actions on a range of effectors, including enterocytes, enteric neurons, vagal sensory neurons and intrinsic primary afferent neurons, blood vessels, lymphocytes, myofibroblasts and the hypothalamus. Through vagal afferents, GLP-1 acts on the brain and mediates satiety. Via further downstream signaling, slowed gastric emptying, inhibition of gastric acid secretion, and the stimulation of insulin release are elicited. L-cells also express interoceptors that receive signals from the internal milieu, including from neurons and hormones. + stimulation, − inhibition, *FFARs* free fatty acid receptors, *GLP* glucagon-like peptide, *IPAN* intrinsic primary afferent neuron, *PYY* peptide YY. (From [7])

briefly summarized, happens as follows: glucose diffuses into the β-cell through the glucose transporter type 2 and is processed to adenosine triphosphate (ATP), which leads to a closure of outward ATP-sensitive potassium channels. This elicits a depolarization of the cell membrane, making it more likely for voltage-dependent calcium channels to open. Intracellular calcium influx is thus enhanced, which is the stimulus for the exocytosis of the insulin carrying vesicles.

The underlying mechanisms how GLP-1 increases insulin secretion in a glucose dependent manner are complex and not yet fully uncovered (details in [8, 9]). In short, glucose-dependent GLP-1 effects happen at several points of the intracellular signal cascades (Fig. 35.3). Binding of GLP-1 to its receptor on the β-cell surface leads to the transformation of ATP to cyclic adenosine monophosphate (cAMP). The higher the blood glucose, the more ATP is available, and thus the more cAMP is produced. Cyclic AMP then activates protein kinase A and another messenger protein, which leads through several further steps to an increase in cytoplasmic free calcium concentrations. That finally triggers exocytosis of insulin-containing vesicles into the bloodstream (Fig. 35.3). Some data also suggest that there are mechanisms

Table 35.1 Organ specific and systemic effects of endogenous GLP-1

	Parameter	Effect
Pancreas	Glucose-dependent insulin secretion of the β-cell	↑
	β-cell proliferation	↑
	Glucagon secretion of the α-cell	↓
	Endogenous GLP-1 secretion in patients with T2D	↓
Brain	Somatostatin secretion	↑
	Satiety	↑
	Hunger	↓
	Energy intake	↓
Gastrointestinal tract	Gastric emptying	↓
	Gastric acid secretion	↓
Heart	Heart rate	↑
Systemic	Blood glucose concentration	↓
	Body weight	↓
	Insulin-sensitivity in patients with T2D	↑

GLP-1 glucagon-like peptide-1, *T2D* type 2 diabetes, ↓ decreases, ↑ increases

how GLP-1 directly increases insulin secretion, independently from the presence of glucose [10]. However, in the clinical use of GLP-1 receptor agonists, these mechanisms seem to be neglectable.

The stimulation of insulin secretion of the β-cell is not the only glucose-lowering effect of GLP-1. GLP-1 also is a strong inhibitor of glucagon secretion from the α-cells of the pancreas, a further mechanism of GLP-1 to lower blood glucose. In patients with type-1 diabetes with C-peptide levels of zero, it was shown that GLP-1 administration also leads to a marked decrease of blood glucose concentration [11]. Which further factors lead to GLP-1 effects on glucose metabolism is subject to current research.

Effects on Intestinal Motility

Another very important physiologic function of GLP-1 and other gastrointestinal hormones (other important ones are peptide YY [PYY] and cholecystokinin [CCK]) is the control of the secretion of digestive enzymes and of gastric and intestinal motility [7]. As described above, intraluminal fats in the distal parts of the ileum bind to fatty acid receptors on the surface of L-cells. This leads to GLP-1 and PYY secretion and via signal transduction from GLP-1 receptors to intestinal nerves and vago-vagal reflexes to the inhibition of gastric emptying and gastric acid secretion. This reflex is termed the ileal break, because nutrients (fats) arriving in the ileum slow the motility of upper parts of the digestive tract.

Effects on the Central Nervous System

In addition to its pancreatic and intestinal location, the GLP-1 receptor is also expressed in many other regions of the human body, suggesting a much broader function than insulinotropic and gastrointestinal effects. From animal data, we know that the GLP-1 receptor is also expressed widely in the brain, with highest concentrations in the hypothalamus, the homeostatic center of the brain. In anaesthetized mice, several experiments using manganese-enhanced magnetic resonance imaging were performed. High dosages of intraperitoneally injected GLP-1, which alike in humans also reduces energy intake in mice, showed significant reductions in signal intensity in nuclei of the hypothalamus, which are known to mediate hunger: similar signal reductions in these regions occurred when animals were fed with food unrestricted in calories [12]. As a further prove of direct intracerebral action of GLP-1, in a study with free-feeding mice, it was shown that the GLP-1 analog liraglutide suppressed food intake and body weight in a dose-dependent manner not only when administered intraperitoneally or IV but also when injected directly into the third cerebral ventricle [13].

Also in humans, the hypothalamus regulates many vegetative processes, including the control of body homeostasis and metabolism. These effects have already been investigated in behavioral experiments, and as well with neuroimaging, mainly with functional magnetic resonance imaging (fMRI), in order to localize brain areas involved in this regulation. In a placebo-controlled fMRI study with 24 obese men, participants had a significant decrease in mean energy intake and hunger ratings after a single dose IV administration of the GLP-1 analog exenatide. It is known that patients can have variable responses to drugs of the GLP-1 analog class, and the effects observed in this study varied strongly among participants. The participants could be divided into two equally sized groups, one with >10% reduction of energy intake and the other with <10% reduction of energy intake through exenatide application. Functional MRI scans of patients given a food picture presentation task showed that the drug increased connectedness of the hypothalamus only in the group where the drug had a >10% reduction of energy intake. In the group where no anorectic effect was observed, no hypothalamic response was seen, suggesting that the anorectic effect of the GLP-1 analog is mediated via the hypothalamus [14]. Other fMRI studies with different experimental designs have shown that also activity in areas of the brain, which are part of the dopaminergic reward system, is altered by GLP-1 infusions [15].

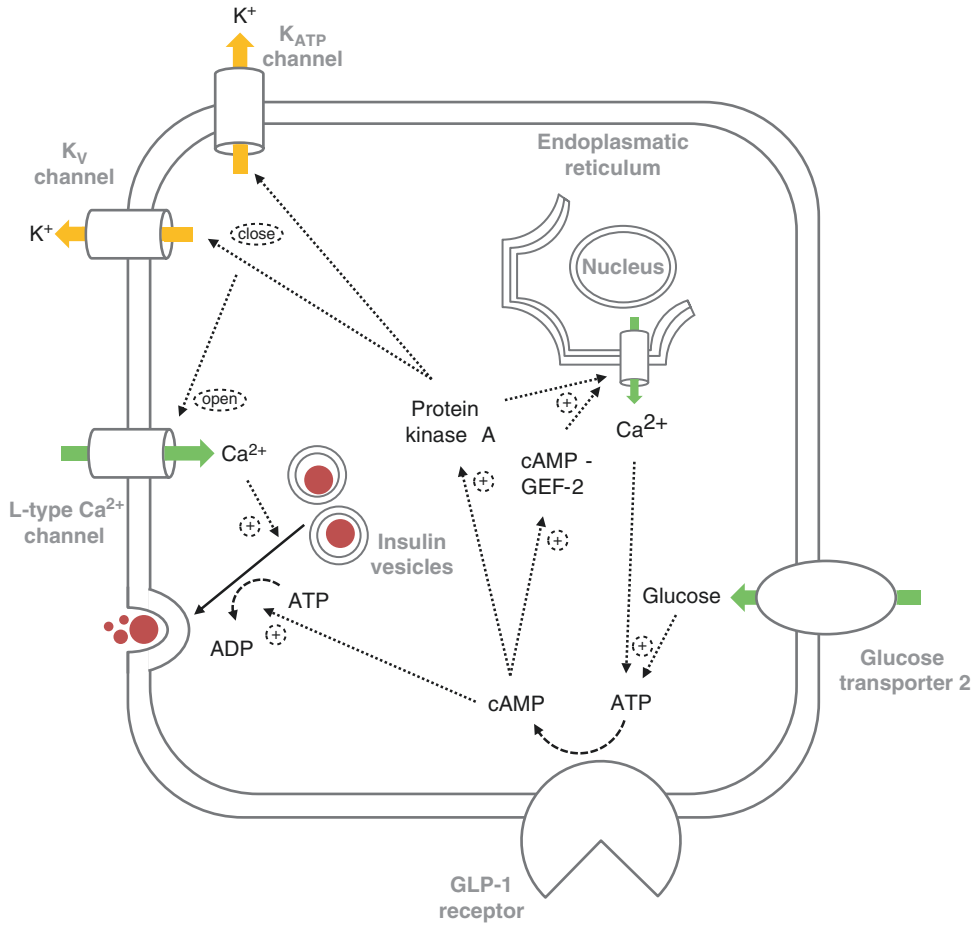

Fig. 35.3 Glucose-dependent insulinotropic glucagon-like peptide-1 (GLP-1) effects in the β-cell. An important mechanism of the glucose dependency of GLP-1 action is mediated via intracellular adenosine triphosphate (ATP) concentrations. The higher the blood glucose level, the more glucose enters the β-cell via the insulin-independent glucose transporter type 2 and is metabolized to ATP. Binding of GLP-1 to the GLP-1 receptor on the β-cell surface stimulates the G-protein of the adenylate cyclase, which results in transformation of ATP to cyclic adenosine monophosphate (cAMP). Cyclic AMP then activates two central proteins responsible for the further transmission of the GLP-1 signal: protein kinase A and cAMP-regulated guanine nucleotide exchange factor 2 (cAMP-GEF-2). Protein kinase A contributes to closing the ATP-sensitive potassium channel (K_{ATP}) and the delayed rectifying potassium channel. Closure of these two outward potassium channels increases intracellular positive potentials and thus facilitates membrane depolarization and opening of inward L-type calcium channels. Increased cytoplasmic free calcium concentrations trigger exocytosis of the insulin containing vesicles. This action is further potentiated by increased cAMP levels. Protein kinase A and cAMP-GEF-2 both trigger calcium release from intracellular stores in the endoplasmic reticulum, again enhancing the calcium dependent actions leading to insulin release. *ADP* adenosine diphosphate, *ATP* adenosine triphosphate, *Ca^{2+}* ionized calcium, *cAMP* cyclic adenosine monophosphate, *cAMP-GEF-2* cAMP-regulated guanine nucleotide exchange factor 2, *GLP-1* glucagon-like peptide-1, *K^+* ionized potassium, *K_{ATP} channel* ATP-sensitive potassium channel, *K_V channel* delayed rectifying potassium channel. (Modified from [8])

Mechanism of Action of GIP

GIP was discovered earlier than GLP-1, and the GIP receptor has been well characterized. However, initial pharmacological studies focused on GLP-1 receptor agonists. The emphasis on GLP-1 therapy derived from several reasons: animal research led to the assumption that GIP administration promoted obesity and impaired lipid metabolism, and human single-dose trials with GIP agonists in patients with T2D found worsened postprandial hyperglycemia. But later investigations of physiologic GIP actions showed that the detrimental GIP effects only occur in hyperglycemia and uncontrolled diabetes. In euglycemia and well-controlled diabetes, GIP receptor activation by GIP analogs has beneficial effects in the human body. There are reports of increased β-cell survival by GIP through signaling pathways independent of GLP-1, supporting the hypothesis that the two incretins are not redundant and may complement one another. GIP research leads to the development of dual GLP-1/GIP co-agonists, of which the first one (tirzepatide) already showed good clinical results in phase 3 studies (see below) [16].

Pharmacological Substances

Exenatide

The first GLP-1 analog approved for the treatment of diabetes was exenatide in 2005 in its formulation, which is administered twice daily, making it the lead substance of the GLP-1 analog class. Exenatide is the synthetic version of exendin-4, a peptide originally isolated from the saliva of the lizard Gila monster. It has an amino acid homology of about 50% with the endogenous human GLP-1 molecule. Mainly due to the substitution of the amino acid alanine in position two by glycine, the molecule is much more resistant to cleavage by DPP-4 than endogenous GLP-1, increasing plasma half-life from 2–5 min to 2.4 h after subcutaneous (SC) administration. It is licensed to be prescribed with or without oral hypoglycemic agents and with or without additional insulin.

Liraglutide

It was followed by the once-daily administered liraglutide in 2009 (Europe) and 2010 (USA). Liraglutide's peptide structure is much closer to the human GLP-1, having a 97% sequence identity with native GLP-1. The molecule binds to human albumin and has a much longer half-life than exenatide of 13–15 h after SC administration. The typical initial dose is 0.6 mg injected SC once daily. The dose can be increased to a maximum of 1.8 mg daily in the treatment of T2D. Because of its weight-reducing effect, the drug was also filed for approval for weight reduction in obesity, also in the absence of diabetes, and got an approval in 2014 (USA) and 2015 (Europe). The dose if used for weight reduction is 3 mg per injection, also applied once daily [17].

In its cardiovascular outcome trial (CVOT) named LEADER [18], the drug met the criteria for cardiovascular safety as defined by the United States Food and Drug Administration (USFDA) (Box 35.1). In the trial, reductions in the primary composite outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) were demonstrated (hazard ratio [HR] 0.87, confidence interval [CI] 0.78–0.97, $p = 0.01$). Furthermore, a decrease in cardiovascular death (HR 0.78, CI 0.66–0.93, $p = 0.007$) and all-cause mortality (HR 0.85, CI 0.74–0.97, $p = 0.02$) as compared to placebo treatment were seen (Table 35.2). The number needed to treat for patients with T2D and high cardiovascular risk to prevent one death (death from any cause) in 3 years was 98 [18].

Table 35.2 Key pharmacological characteristics and cardiovascular outcome data of GLP-1 receptor agonists

Drug	Molecular properties	$T_{1/2}$	Dosing	CVOT	Reduction in prim. Comp. outc./CV mortality/ all-cause mortality	Specifications of CVOT	Reduction in HbA1c[a] (in percentage points HbA1c)	Reduction in body weight[a]
Exenatide	39-AA peptide	2.4 h	SC, 5 and 10 µg, *b.i.d.*	None	N.a.	N.a.	N.a.	N.a.
Liraglutide	97% structural homology with native GLP-1	12 h	SC, 1.2 and 1.8 mg, *o.d.*	LEADER [18]	**Yes** (HR 0.87, CI 0.78–0.97, $p = 0.01$/ **Yes** (HR 0.78, CI 0.66–0.93, $p = 0.007$)/ **Yes** (HR 0.85, CI 0.74–0.97, $p = 0.02$)	Initial treatment group $n = 4668$, median treatment duration 3.2 y, prim. comp. endp.: death from CV causes, nonfatal myocardial infarction, nonfatal stroke	0.4%	2.3 kg
Exenatide LAR	Polyglactin microspheres releasing exenatide	96 h	SC, 2 mg, once weekly	EXSCEL [19]	**No** (HR 0.91, CI 0.83–1.00, $p = 0.06$)/ **No** (HR 0.88, CI 0.76–1.02)/ **No** (HR 0.86, CI 0.77–0.97[b])	Initial treatment group $n = 7356$, median treatment duration 3.2 y, prim. comp. endp.: death from CV causes, nonfatal myocardial infarction, nonfatal stroke	0.5%[c]	1.3 kg[c]

(continued)

Table 35.2 (continued)

Drug	Molecular properties	$T_{1/2}$	Dosing	CVOT	Reduction in prim. Comp. outc./CV mortality/ all-cause mortality	Specifications of CVOT	Reduction in HbA1c[a] (in percentage points HbA1c)	Reduction in body weight[a]
Dulaglutide	GLP-1 peptide fused to IgG	90 h	SC, 0.75 and 1.5 mg, once weekly	REWIND [20]	**Yes** (HR 0.88, CI 0.79–0.99, $p < 0.05$)/ **No** (HR 0.91, CI 0.78–1.06, $p = 0.21$)/ **No** (HR 0.90, CI 0.80–1.01; $p = 0.067$)	Initial treatment group $n = 4949$, median treatment duration 5.4 y, prim. comp. endp.: death from CV causes, nonfatal myocardial infarction, nonfatal stroke	0.6%[c]	1.5 kg[c]
Lixisenatide	44-AA derivative of exenatide	4 h	SC, 10 and 20 µg, *o.d.*	ELIXA [21]	**No** (HR 1.02, CI 0.89–1.17)/ **No** (HR 0.98, CI 0.78–1.22)/ **No** (HR 0.94, CI 0.78–1.13)	Initial treatment group $n = 3034$, median treatment duration 1.9 y, prim. comp. endp.: death from CV causes, nonfatal stroke, nonfatal myocardial infarction, unstable angina	0.3%[b]	0.7 kg[b]
Semaglutide SC	94% structural homology with native GLP-1	1 week	SC, 0.5 and 1.0 mg, once weekly	SUSTAIN-6 [22]	**Yes** (HR 0.74, CI 0.58–0.95, $p = 0.02$)/ **No** (HR 0.98, CI 0.65–1.48)/ **No** (HR 1.05, CI 0.74–1.50)	Initial treatment group $n = 1648$, median treatment duration 2.1 y, prim. Comp. Endp.: Death from CV causes, nonfatal myocardial infarction, nonfatal stroke	1.0%	4.3 kg
Oral semaglutide	Very low bioavailability (~1%), very variable; despite long plasma $t_{1/2}$ daily intake recommended	1 week	Oral, 3, 7, and 14 mg, *o.d.*	PIONEER 6 [23]	**No** (HR 0.79, CI 0.57–1.11, $p = 0.17$)/ **Yes** (HR 0.49, CI 0.27–0.92)/ **Yes** (HR 0.51, CI 0.31–0.84)	Initial treatment group $n = 1591$, median treatment duration 1.3 y, prim. comp. endp.: death from CV causes, nonfatal myocardial infarction, nonfatal stroke	0.7%	3.4 kg
Efpeglenatide[d]	Modified exendin-4 molecule conjugated with IgG4 F_c fragment	1 week	SC, studies with 4 and 6 mg, once weekly	AMPLITUDE-O [24]	**Yes** (HR 0.73, CI 0.58–0.92), $p < 0.01$)/ **No** (HR 0.72, CI 0.50–1.03)/ **No** (HR 0.78, CI 0.58–1.06)	Initial treatment group $n = 2717$, median treatment duration 1.8 y, patients with very high CV risk, two different dose groups[e]; prim. comp. endp.: death from CV or undetermined causes, nonfatal myocardial infarction, nonfatal stroke	1.2%[c]	2.6 kg[c]

AA amino acid, *b.i.d.* bis in die, twice daily, *CI* 95% confidence interval, *CV* cardiovascular, *CVOT* cardiovascular outcome trial, F_c fragment crystallizable, *GLP-1* glucagon-like peptide-1, *HbA1c* hemoglobin A1c, *IgG* immunoglobulin G, *LAR* long acting release, *max* maximum, *n.a.* not applicable, *o.d.* omni die, once daily, *outc.* outcome, *prim. Comp. endp.* primary composite endpoint, *SC* subcutaneously, $t_{1/2}$ half-life, *y* years

[a]Data from CVOT, adjusted for placebo, for highest dose group, respectively, until the end of study (if not otherwise specified)

[b]Not considered to be statistically significant by authors based on the hierarchical testing plan (i.e., if significant difference was not found for an outcome, formal hypothesis testing was not to be conducted for lower ordered outcomes. Prim. comp. outc. was ranked higher than all-cause mortality); Average above all study visits

[c]Least-squares mean

[d]Not yet approved

[e]1:1 ratio, in publication results reported together as one mean value

Of note, additional monitoring of liraglutide was demanded by regulatory authorities because of a significant increase of medullary thyroid cancer in animals treated with the drug. This risk could not yet be fully ruled out in humans, probably due to the very low incidences of medullary thyroid cancer in observed populations.

Exenatide LAR

In 2011, a long-acting formulation of exenatide was approved for the therapy of T2D and termed exenatide long-acting release (LAR). The exenatide molecule is attached to so-called microspheres, small particles in the case of exenatide LAR of 0.06 mm size. The exenatide LAR microspheres are made of molecules of lactic and glycolic acid (poly-lactic-co-glycolic acid), which is the most common material from which microspheres are prepared. The drug is loaded onto the surface of and into the microsphere and then released as the matrix materials degrade. The characteristics of the binding of the molecule on the surface and the internalization into the microsphere explain the suboptimal pharmacokinetics of exenatide LAR: in the first 2 days after SC application, exenatide plasma concentrations increase rapidly. This rapid absorption of the molecule is due to the loosely bound exenatide on the surface of the microspheres. The internalized drug from inside the vesicles is not released until 2 weeks later. It takes up to 7 weeks for the drug to be completely released [25]. In the CVOT, the EXSCEL trial, initially >7000 patients with T2D were treated for up to 5 years, and the mean treatment duration was 3.1 years. A primary composite outcome event (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) occurred in 11.4% of patients in the exenatide LAR group versus 12.2% patients in the placebo group (HR 0.91, CI 0.83–1.00, $p = 0.06$ for superiority) [19]. Thus, the drug proved to be safe, but could not statistically significantly show a significant benefit on cardiovascular outcome despite the high number of included patients.

Dulaglutide

Dulaglutide was the next once-weekly GLP-1 analog approved for diabetes treatment. USFDA approval was granted in 2014. To yield a pharmacokinetic, which allows a once weekly application, a molecule with 90% amino acid sequence homology to endogenous human GLP-1 is linked to an F_c fragment of human immunoglobulin G4 (IgG4). The F_{ab} fragments are substituted by two GLP-1 molecules; at each of the two F_c parts of the heavy chains, one GLP-1 molecule is bound. Binding to the F_c parts of IgG slows absorption due to the larger molecular size. The designed molecule is relatively resistant to degradation by DPP-4, and renal clearance is slowed. After a single SC administration, maximum serum concentrations are reached after about 2 days. Steady-state concentrations are achieved between 2 and 4 weeks after once-weekly administration.

In the CVOT REWIND, after a very long mean treatment duration of 5.4 years, the primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes (including unknown causes) occurred 12.0% of participants in the dulaglutide group and in 13.4% of participants of the placebo group (HR 0.88, CI 0.79–0.99, $p < 0.05$). All-cause mortality did not differ significantly between groups (10.8% vs. 12.0%, HR 0.90, CI 0.80–1.01; $p = 0.067$). In the dulaglutide group, 47.4% of participants reported a gastrointestinal adverse event compared with 34.1% during placebo treatment ($p < 0.0001$). At the end of the trial, hemoglobin A1c (HbA1c) in the drug group was 0.6% points lower than in the placebo group ($p < 0.0001$), and body weight was 1.5 kg lower ($p < 0.0001$) [20].

Lixisenatide

A further GLP-1 analog was approved in 2016 for the US American market: lixisenatide. It is a polypeptide consisting of 44 amino acids with a single proline substitution and a modified C-terminus of six lysine molecules. Its chemical structure makes it more resistant to degradation by DPP-4 than exenatide and needs to be injected once daily. Still, with a plasma half-life of 2.7–4.3 h, it is removed from circulation much faster than liraglutide, which is also administered once daily. The CVOT of lixisenatide was named ELIXA [21]. A total of 6068 patients with T2D and a history of myocardial infarction (83%) or hospitalization for unstable angina (17%) within the last 6 months were randomized to lixisenatide or placebo treatment. The primary composite endpoint consisted of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina. In the *verum* group, during the time of observation, an endpoint occurred in 406 patients (13.4%) and in the placebo group in 399 patients (13.2%) (HR 1.02, CI 0.89–1.17). Thus, in this study, no superiority to placebo could be demonstrated, but cardiovascular safety was proven for lixisenatide during the initial 2 years of treatment of patients with T2D and very high cardiovascular risk. In Europe, the drug was also approved for clinical use, but, for example, in Germany, the drug is not available as a single compound because government and health insurances did not see an additional benefit compared to already existing GLP-1 analogs. However, in 2020, a fixed combination drug of lixisenatide and insulin glargine was introduced to the German market.

Semaglutide

The latest GLP-1 analog approved for clinical usage is semaglutide. It shares a 94% structural homology with native GLP-1 and has a similar molecule structure as liraglutide but is more stable in the human body because it is less susceptible to degradation by DPP-4. Its plasma half-life is about 1 week, and the drug is administered once weekly. In the phase 3 CVOT named SUSTAIN [22] SC applied semaglutide significantly improved glycemic control during the 2 years of treatment. HbA1c was reduced by 0.7% points in the lower-dose group (0.5 mg semaglutide once weekly) and by 1.0% points in the higher-dose group (1.0 mg once weekly). The drug also reduced bodyweight significantly by 2.9 kg compared to placebo in the 0.5 mg group and by 4.3 kg compared to placebo in the 1.0 mg group. Side effects were similar compared to other GLP-1 analogs already on the market. The cardiovascular profile was noninferior to placebo. Gastrointestinal disorders such as nausea, vomiting, and diarrhea occurred more frequently in the treatment group, as expected for a drug of the GLP-1 analog class (51.5% of treated patients with 0.5 and 1.0 mg vs. 35.5% for placebo). In 11.5% of the 0.5 mg and 14.5% of the 1.0 mg groups, treatment had to be stopped due to gastrointestinal disorders versus 5.7 and 7.6% for placebo.

As known from all drugs of the GLP-1 analog class, pulse rate was increased by the medication. The mean heart rate in the treatment group, compared to placebo, increased by 2.0 bpm for 0.5 mg and by 2.5 bpm for 1.0 mg ($p < 0.001$ for both comparisons). Another important negative effect of the treatment was an increase in retinopathy complications (e.g., vitreous hemorrhage or blindness). Diabetic retinopathy complications occurred in 50 patients (3.0%) of the semaglutide group and only in 29 (1.8%) of the placebo group (HR 1.76, CI 1.11–2.78, $p = 0.02$). The authors of the study suggest that the rapid lowering of blood glucose concentrations in the treatment group might be an explaining factor, but cannot rule out direct drug-related effects. Lipase and amylase levels were significantly higher in the semaglutide group than in the placebo group, but acute pancreatitis occurred more frequently in the placebo group than in the semaglutide group (12 vs. 9 events).

In this CVOT, after 2 years of treatment, there was no significant reduction in all-cause mortality (3.8% in the treatment group vs. 3.6% in the placebo group) or cardiovascular mortality (2.7 vs. 2.8%). However, there was a significant reduction in the composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke of 6.6 versus 8.9% (HR 0.74, CI 0.58–0.95, $p = 0.02$ for superiority) [22]. The injectable drug was approved for the treatment of T2D in 2017 in the United States and in 2018 in the European Union, Canada, and Japan.

Semaglutide is the first GLP-1-analog; also an oral preparation was approved, about 2 years after the SC drug. The oral version is co-formulated with an "absorption enhancer," a molecule that causes a localized increase in pH. This leads to an increased solubility of the drug and to a decreased enzymatic activity in its close environment, thus protecting the drug from intragastric enzymatic degradation. The CVOT PIONEER-6 demonstrated noninferior cardiovascular safety of oral semaglutide versus placebo, but could not show superiority. The hazard ratio of the primary outcome, a composite of death from cardiovascular, causes nonfatal myocardial infarction or nonfatal stroke, after about 1.5 years of trial duration was 0.79 (CI 0.57–1.11). The HbA1c was reduced by 0.7% points as compared to placebo, and body weight was reduced by 3.4 kg [23].

Just like for liraglutide, also for semaglutide, a preparation including also a higher dosage was approved under a different brand name for the treatment of obesity, also in the absence of T2D. In the phase 3 study (SELECT), overweight and obese patients without a history of diabetes are treated for 2.5–5 years with the drug. The primary outcome measure is the occurrence of a composite endpoint consisting of CV death, nonfatal myocardial infarction, or nonfatal stroke. The study is the first CVOT to evaluate superiority in major adverse cardiovascular events reduction for an antiobesity medication. It is expected to be completed by the end of 2023 [26].

Efpeglenatide

Efpeglenatide is a GLP-1 analog consisting of a modified exenatide molecule attached to the F_c fragment of IgG (similar to the IgG modification of dulaglutide). At the time of the research for this book chapter, approval was not yet granted, but in 2021 data of the phase 3 trial, AMPLITUDE-O was published. During a median follow-up of 1.8 years, a major adverse cardiac even occurred in 7.0% of participants in the efpeglenatide group and 9.2% of the placebo group (HR 0.73, CI 0.58–0.92, $p < 0.001$ for noninferiority, $p < 0.01$ for superiority). Adjusted for the placebo treatment group, HbA1c was reduced by 1.2% points in the efpeglenatide group and body weight by 2.6 kg (both statistically significant). With these data, efpeglenatide is the first derivative of exendin-4 to demonstrate positive cardiovascular outcomes [24]. In a short 16 weeks phase 2 study, efpeglenatide was also beneficial and safe when administered in a higher dose only once a month. Further studies are needed to evaluate the long-term efficacy and safety of efpeglenatide once monthly [27].

Tirzepatide

Tirzepatide is the first incretin drug applied for approval in the United States and the EU (in 2021) using a dual incretin receptor agonism. The compound is an analog of human GIP, which was modified to also activate the GLP-1 receptor, but to a lesser extent than the GIP receptor. It is injected once weekly SC. The phase 3 trials are conducted under the study name SURPASS. In the latest trial, tirzepatide was tested in patients with T2D and medication with insulin glargine. Mean HbA1c reduction after 40 weeks of tirzepatide treatment adjusted for placebo effects was −1.5% points in the two groups with the highest dosages (for both groups $p < 0.001$). Mean body weight change from baseline was −9.1 and −10.5 kg in the two mentioned groups (both $p < 0.001$). The most common treatment-emergent adverse events in the tirzepatide groups versus placebo group were diarrhea (12–21% vs. 10%) and nausea (13–18% vs. 3%) [16]. The CVOT SURPASS-CVOT is estimated to be completed by the end of 2024.

Comparisons of Clinical Data from Available Trials and Discussion of Clinical Effects

GLP-1 analogs proved to decrease HbA1c and body weight in long-term treatment (example for liraglutide 3 mg in Fig. 35.4). The mean reduction in HbA1c of 0.75–1.5% in the first half year of treatment in phase 3 and CVOTs is seen in all drugs of this class. But as inclusion criteria and study protocols of the clinical studies are not consistent, a direct comparison of the substances is not possible with these data.

To compare substances, head-to-head trials have been conducted comparing HbA1c and body weight lowering effects of GLP-1 analogs. The once weekly formulation of exenatide was found to reduce HbA1c stronger than the twice daily formulation, and liraglutide 1.8 mg was superior to both formulations; however, differences were small (0.2 and 0.3% points lower HbA1c). There were no differences in HbA1c reduction between liraglutide 1.8 mg and dulaglutide. Lixisenatide was not inferior to exenatide twice daily, but inferior to liraglutide 1.8 mg (again small differences in HbA1c effects) [29]. The SUSTAIN 7 study compared semaglutide with dulaglutide. It found HbA1c reductions of 1.8% points for semaglutide 1.0 mg vs. 1.4% points for dulaglutide 1.5 mg. Patients taking semaglutide also lost more weight than those taking the equivalent dose of dulaglutide [30]. Also in trials comparing semaglutide 1.0 mg with exenatide LAR and liraglutide 1.2 mg, semaglutide was superior in HbA1c and weight reduction [31]. In the STEP 8 study, the weight loss efficacy of semaglutide 2.4 mg in patients without diabetes was tested against the daily injectable liraglutide 3 mg. The study showed a significantly greater average body weight reduction of 15 kg with semaglutide, compared with 7 kg under liraglutide 3 mg [32].

Also with the not yet approved GLP-1/GIP co-agonist tirzepatide, a comparator trial with semaglutide has been published (SURPASS-2). HbA1c reductions of up to 2.3% points during 40 weeks of tirzepatide treatment were significantly greater than the 1.9% point reduction achieved with semaglutide. Tirzepatide also resulted in significantly greater weight reductions, of up to 5.5 kg more than seen with semaglutide [33]. We did not report about the GLP-1 analog albiglutide, for which CVOTs and comparator studies have been

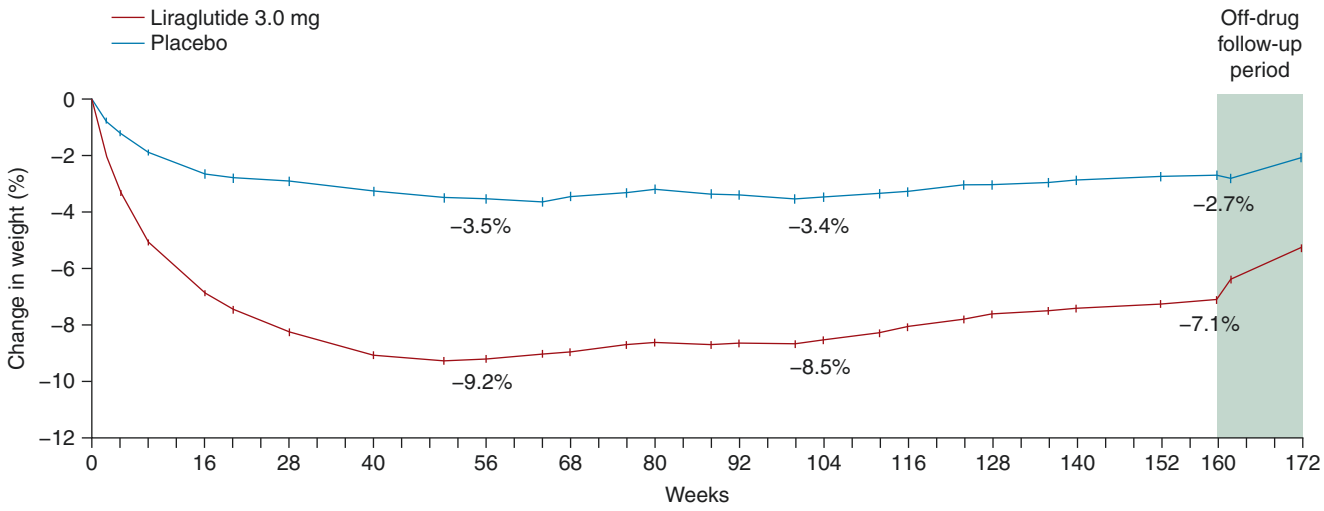

Fig. 35.4 Mean relative change in bodyweight for participants in a randomized, double-blind trial with liraglutide 3 mg and placebo during 3 years of treatment. Data shown are the observed means (with standard error) of the full-analysis set (patients who completed each scheduled visit). * $p < 0.0001$. (From [28])

performed, because in 2017 and 2018, the manufacturer withdrew the drug from worldwide markets, according to their own information for economic reasons.

To sum up GLP-1 analog comparator studies, of today's available GLP-1 agonists, semaglutide seems to be the most effective in terms of HbA1c reduction in T2D and in weight reduction. The GLP-1/GIP co-agonist tirzepatide seems to have an even higher efficacy than semaglutide and may improve pharmacological T2D and obesity treatment if approved.

As of today, the available drugs with a reduction in the primary composite cardiovascular endpoint are liraglutide, dulaglutide, and semaglutide after SC injection. A reduction of cardiovascular and all-cause mortality was found for liraglutide and oral semaglutide. An overview about cardiovascular outcome data of GLP-1 analogs can be seen in Fig. 35.5 and in Table 35.2.

The differences in blood glucose control between the pharmacologic agents cannot explain why liraglutide, dulaglutide, and semaglutide, but not lixisenatide and exenatide LAR, had positive cardiovascular outcomes. Different study designs may well be the cause for these discrepancies. However, it cannot be ruled out that there are different beneficial effects of the drugs with positive cardiovascular outcome than mere lowering of blood glucose. Or lixisenatide and exenatide LAR cause other negative effects regarding cardiovascular events but were not identified in available clinical trials.

Pipeline of Incretin-Based Substances for Diabetes and Obesity Treatment

Due to the elegant mechanism of utilizing physiological incretin receptor pathways in the treatment of T2D and obesity, the drug development pipeline of potential incretin-based candidates is full. Today, the greatest interest lies in the development of substances activating two (like tirzepatide), or even more, different incretin receptor types simultaneously.

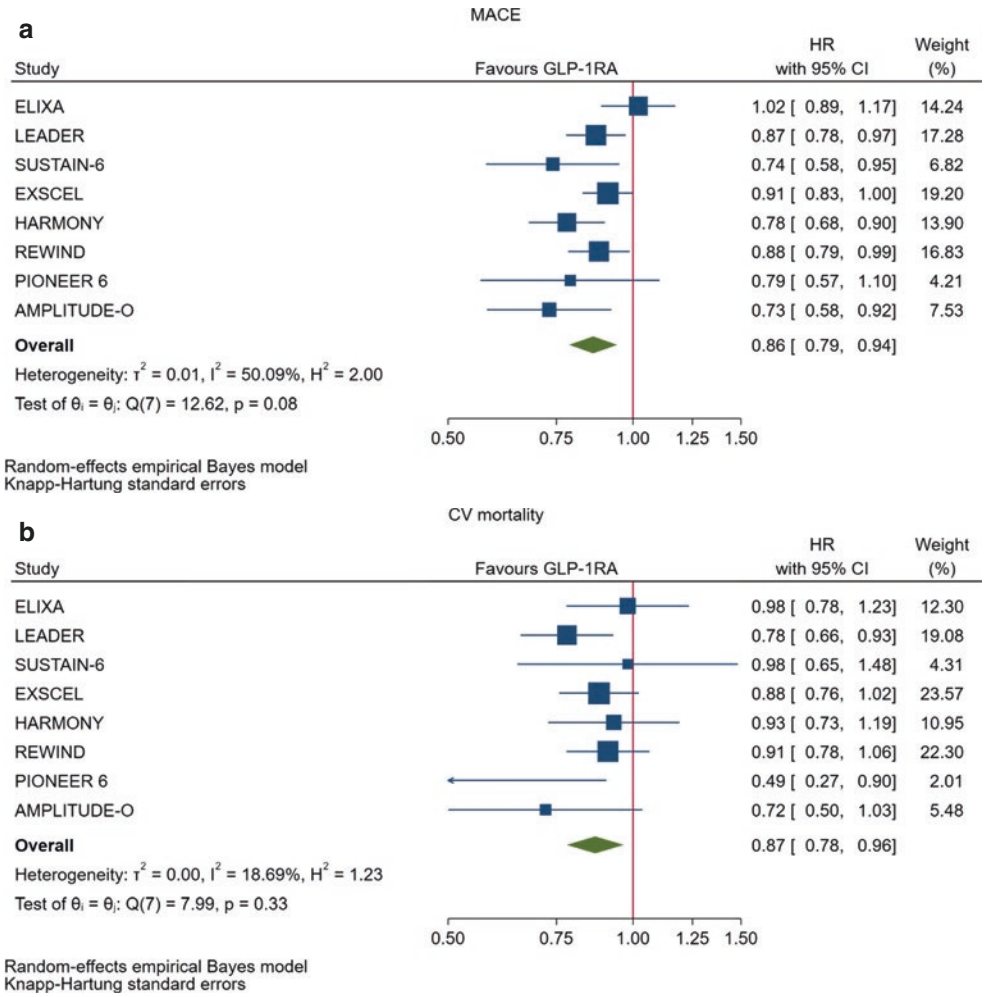

Fig. 35.5 Forest plots of the meta-analysis of cardiovascular outcome trials with GLP-1 receptor agonists versus placebo treatment on major cardiovascular events (**a**) and cardiovascular mortality (**b**). The results are expressed as hazard ratio (HR). For study active components and other specifications, see Table 35.2. *CI* confidence interval, *CV* cardiovascular, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *MACE* major cardiovascular events. (From [34])

An interesting candidate is cotadutide, a dual receptor agonist based on the molecular structure of oxyntomodulin, which is another gastrointestinal peptide that is as GLP-1 physiologically secreted from the L-cells of the intestine after oral nutrient uptake. Cotadutide activates both the GLP-1 and the glucagon receptor with similar activity. The drug developers suggest that the blood glucose-increasing effect of glucagon is compensated by the glucose-lowering action of GLP-1 but that the glucagon agonism leads to appetite suppression and further weight loss. A phase 2b trial in overweight and obese patients with T2D with daily SC injections of the drug was already published. Weight loss after 1 year of treatment in the high-dose group was −4.3% of the baseline weight (placebo-adjusted) and higher than in the comparator study group with single GLP-1-activation through liraglutide 1.8 mg with only −2.6% of bodyweight. HbA1c reduction in the cotadutide high-dose groups was −0.7% points (placebo-adjusted) and similar to the liraglutide group [35].

Another promising target for diabetes and obesity treatment is the CCK receptor 1. CCK is another gastrointestinal peptide hormone secreted from enteroendocrine cells of the duodenum in response to a meal. Its physiologic functions include the inhibition of gastric emptying, the stimulation of exocrine pancreatic secretion, and the stimulation of production and secretion of bile. A dual GLP-1 and CCK receptor co-agonist showed in diabetic mice enhanced beneficial effects on HbA1c, glucose tolerance, and pancreas function restoration as compared with semaglutide [36].

Clinical development also started with a compound with agonism on three peptide receptors: on the GLP-1, the glucagon, and the GIP receptor. The investigated substance, which was not yet given a commercial name, is structurally based on the exendin-4 sequence. It was then modified to also significantly activate the glucagon and the GIP receptor and to avoid cleavage through DPP-4. Studies in obese mice and in monkeys showed enhanced effects on each of the metabolic outcomes, superior to those achieved with dual GLP-1/glucagon receptor agonists. In the first-in-man (phase I) study, the compound was well tolerated, and further clinical trials can be expected [37].

Side Effects of the GLP-1 Analog Class

Side effects of GLP-1 analogs—unlike classical off-target adverse effects as known from other drugs (like, e.g., muscle and joint pain in statin therapy)—include physiological effects of GLP-1 receptor activation. The most pronounced side effect is gastrointestinal intolerability. This includes abdominal fullness, meteorism, belching, flatulence, nausea, and vomiting. In the semaglutide CVOT, the placebo-adjusted rate of gastrointestinal symptoms was 16%. A further frequently discussed side effect of GLP-1 analogs is the increased risk of pancreatitis. Shortly, after market introduction of exenatide, the USFDA issued an alert reporting 30 cases of pancreatitis associated with the drug. Several post market surveillance studies have followed up on this issue, and the debate is still ongoing whether GLP-1 analogs (and DPP-4 inhibitors) increase the risk of pancreatitis. Currently, existing data does not support increased risks of pancreas damage due to GLP-1 analogs or DPP-4 inhibitors. In a meta-analysis combining all available GLP-1 analog CVOT data, a hazard ratio of 1.05 (CI 0.78–1.40) was found for pancreatitis and 1.12 (CI 0.77–1.63) for pancreatic cancer [38]. However, especially for pancreatic cancer, the follow-up duration of those trials ranging from a median of 1.3 to 5.4 years may not be long enough for already giving an all-clear signal.

DPP-4 Inhibitors

An alternative way of utilizing the beneficial incretin effects on glucose metabolism is inhibiting the GLP-1 degrading enzyme DPP-4 and thus prolonging endogenous GLP-1 plasma half-life. However, the glucose-lowering effect of DPP-4 inhibitors is much smaller than the effect of a direct agonism on the GLP-1 receptor elicited with GLP-1 analogs. The first DPP-4 inhibitor approved for the treatment of diabetes was sitagliptin in 2006. Indication for prescription is poor glycemic control in T2D. It has to be prescribed in combination with diet and exercise, with or without other oral hypoglycemic agents and with or without insulin. Available tablets are of 25, 50, and 100 mg, and there are fixed combinations with other oral antidiabetic drugs available. The usual sitagliptin dose in adults with good renal function is 100 mg once daily. Adverse reactions occur seldom and include headache, nausea, and rash. Hypoglycemia can occur if treatment is combined with other blood glucose-lowering drugs. Excretion happens mainly unchanged, and only about 15% of the drug is metabolized in the liver, largely by the cytochrome P450 system (CYP3A4 and 2C8), making liver injury by the drug a rare side effect. A CVOT was performed (named TECOS) and proved cardiovascular safety [39].

In 2007, the second DPP-4 inhibitor was approved for the treatment of T2D, vildagliptin, and in 2009, the third drug of this class was approved, saxagliptin. However, in the cardiovascular outcome study for saxagliptin with T2D patients at increased risk for cardiovascular disease (SAVOR-TIMI [40]), there was a warning sign for increased mortality as compared to placebo treatment: there was a trend for an increase in all-cause mortality (HR 1.11, CI 0.96–1.27) based on about 800 observed deaths, which was driven by non-cardiovascular deaths [40]. Furthermore, the study showed a statistically significant 27% increased rate for hos-

pitalization due to heart failure in the drug group: 3.5% of patients who were treated with saxagliptin were hospitalized for heart failure compared to only 2.8% of patients treated with placebo (HR 1.27, CI 1.07–1.51, $p = 0.007$). In 2015, the USFDA released a warning stating "*A potential increase in all-cause mortality with saxagliptin was observed*." A later large retrospective cohort analysis could not find an increased risk of heart failure for saxagliptin compared with the use of other antidiabetic drugs [41], and the CVOTs of the DDP-4 inhibitors sitagliptin, alogliptin, and linagliptin did not find an increased risk for heart failure for these three substances. The debate about the SAVOR-TIMI results is still ongoing.

Many other chemical compounds have been developed up-to-date inhibiting DPP-4 by variable molecular mechanism. Approval status in the different countries differs, and many of the substances are only approved in either Asian countries, the European Union, or the United States. Among DPP-4 inhibitors approved for the treatment of T2D in the United States, implying the conduction of a cardiovascular outcome study, alogliptin, the cardiovascular outcome study is called EXAMINE [42]. Another DPP-4 inhibitor approved for T2D treatment is linagliptin, the study name CARMELINA [43]. For gemigliptin, anagliptin, teneligliptin, trelagliptin, omarigliptin, and evogliptin, currently no (cost and time intensive) cardiovascular outcome studies are planned, and accordingly, no approval in countries requiring these studies will be possible.

The effects of DPP-4 inhibitors on HbA1c are modest. In the four placebo-controlled CVOTs mentioned above, HbA1c reduction versus placebo was 0.2–0.4% points. Significant reductions in body weight did not occur. Favorable effects of DPP-4 inhibitors on all-cause mortality, cardiovascular mortality, myocardial infarction, or stroke in patients with T2D could not be demonstrated up to date [44].

Concluding Remarks

- GLP-1 analogs reduce HbA1c and body weight of patients with type 2 diabetes consistently in clinical studies. In CVOTs, HbA1c was reduced between 0.3 and 1.0% points, body weight by about 0.7–4.3 kg compared to placebo. After an initial decrease in both parameters, in about the first half year of treatment plateau is reached, and treatment needs to be continued to maintain this effect.
- For liraglutide, dulaglutide, and semaglutide, positive results of CVOTs are available: liraglutide reduced the primary composite cardiovascular, as well as cardiovascular mortality and all-cause mortality. Dulaglutide reduced the occurrence of the primary composite cardiovascular endpoint, semaglutide in the SC formulation the occurrence of the primary composite endpoint and in the oral formulation cardiovascular and all-cause mortality.
- The most common side effects of GLP-1 analogs are dyspeptic complaints including abdominal fullness, meteorism, belching, flatulence, nausea, and vomiting. In <10% of patients, these complaints led to a discontinuation of treatment in clinical studies. Still under review are reports of pancreas damage and of medullary thyroid carcinoma. But as seen from current data, it is rather unlikely that these events in the studies were related to GLP-1 agonist treatment.

Box 35.1 Cardiovascular Outcome Trials (CVOTs)

The United States Food and Drug Administration (USFDA) issued a declaration in 2008 that all new diabetes drugs have to rule out an excess cardiovascular risk. This decision was driven by the high prevalence of cardiovascular disease in diabetes (accounting for approximately 70% of deaths) and by concerns about a study claiming an increased cardiovascular risk for rosiglitazone, which was published shortly before [45]. In these cardiovascular outcome trials (CVOTs), cardiovascular safety is defined by the USFDA as an upper bound of the two-sided 95% confidence interval for major adverse cardiovascular events of less than 1.8 preapproval and 1.3 postapproval. Furthermore, CVOTs are used to analyze if groups treated with new diabetes drugs show statistically significantly less cardiovascular events groups treated with than placebo.

Multiple Choice Questions

1. How do GLP-1 analogs exert their blood glucose-lowering effect? By.
   (a) Increasing **insulin secretion of the pancreatic β-cell**
   GLP-1 analogs bind to the GLP-1 receptor expressed on the surface of pancreatic β-cells and stimulate the adenylyl cyclase pathway, resulting in increased insulin synthesis and increased release of insulin.
   (b) Directly acting on glucose transporters (GLUT-family)
   (c) Blocking the sodium/glucose cotransporter 2 (SGLT-2) in the kidney
   (d) Inhibiting the enzyme alpha-glucosidase in the intestine
   (e) Inhibiting the enzyme dipeptidyl peptidase-4 (DPP-4)

2. Which effects are *not* known for GLP-1 analogs?
   (a) Increasing insulin secretion
   (b) Reducing blood glucose concentrations when elevated
   (c) Promoting satiety
   (d) Decreasing intestinal motility
   (e) **Reducing pulse rate**
   GLP-1 analogs do not reduce pulse rate. On the contrary, in clinical studies, a slight increase in pulse rate has been noted in GLP-1 treated patients.
3. What was the average HbA1c change yielded by GLP-1 analog therapy in type 2 diabetes in the cardiovascular outcome trials?
   (a) Increase of more than 1.0 percentage points
   (b) Increase of >0–1.0 percentage points
   (c) No change in HbA1c
   (d) **Decrease of > 0–1.0 percentage points**
   In approval studies, GLP-1 analogs reduced HbA1c compared to placebo treatment between 0.3 and 1.0 percentage points (Table 35.2).
   (e) Decrease of more than 1.0 percentage points
4. Which of the following diabetes drugs does *not* directly bind to the GLP-1 receptor?
   (a) Exenatide
   (b) **Sitagliptin**
   Sitagliptin is an inhibitor of the dipeptidyl peptidase 4 (DPP-4) and does not directly bind to the GLP-1 receptor.
   (c) **Dulaglutide**
   (d) Liraglutide
   (e) **Semaglutide**
5. Which of the following answers is *not* a typical side effect of the GLP-1 analog class?
   (a) Nausea
   (b) Increase in pulse rate
   (c) **Hypoglycemia**
   Due to the glucose dependent insulinotropic effect of GLP-1, hypoglycemias are not a typical side effect of GLP-1 analogs.
   (d) Diarrhea
   (e) **Vomiting**
6. For which of the following GLP-1 analog preparation a reduction in all-cause mortality could be demonstrated?
   (a) Semaglutide SC
   (b) Lixisenatide
   (c) **Liraglutide**
   For liraglutide in the cardiovascular outcome trial, a reduction in all-cause mortality was demonstrated.
   (d) **Exenatide** LAR
   (e) **Dulaglutide**
7. What is the mechanism how in exenatide LAR plasma half-life is prolonged?
   (a) **Attachment to and incorporation in so-called microspheres.**
   The long-acting formulation of exenatide (exenatide LAR) was created by binding the exenatide molecule to the surface of a microsphere and by incorporating the molecule into the microsphere. This prolongs the absorption of the exenatide molecule after SC application.
   (b) **Binding** of exenatide to human albumin
   (c) **Expression** of exenatide by body cells after mRNA injection
   (d) **Increasing** the exenatide concentration in the drug solution
   (e) Binding of exenatide to an absorption enhancer
8. Which of the following GLP-1 analogs is injected twice daily?
   (a) **Exenatide**
   Exenatide is injected twice daily in the treatment of type 2 diabetes
   (b) **Liraglutide**
   (c) **Dulaglutide**
   (d) **Exenatide** LAR
   (e) **Semaglutide**
9. Which of the following GLP-1 analogs was approved for the treatment of obesity also in the absence of type 2 diabetes?
   (a) Exenatide
   (b) **Liraglutide**
   Liraglutide in the formulation of 3 mg, injected once daily was approved for the treatment of obesity also in the absence of type 2 diabetes
   (c) **Dulaglutide**
   (d) **Exenatide** LAR
   (e) **Lixisenatide**
10. For which of the following GLP-1 analogs an oral formulation is available?
   (a) Exenatide
   (b) Liraglutide
   (c) Dulaglutide
   (d) **Semaglutide**
   Semaglutide is approved in an oral formulation taken once daily.
   (e) Lixisenatide

Further Reading

Furness JB, et al. (2013) The gut as a sensory organ. Nat Rev Gastroenterol Hepatol 10(12):729-40.

- This review provides a fantastic overview about the molecular mechanism how the gut sensors the content of the intestinal lumen and how this information is fur-

ther processed to elicit reactions in the human body. This review also provides further information about the receptors on intestinal L-cells, which, when activated, trigger GLP-1-secretion.

Holst JJ, et al. (2022) Actions of glucagon-like peptide-1 receptor ligands in the gut. Br J Pharmacol. 179(4):727-742.

- Very comprehensive review highlighting GLP-1 physiology with detailed descriptions how GLP-1 and GLP-1 receptor ligands act on the gut and lead to its effects on pancreas, liver, and other parts of the body.

Giugliano D, et al. (2021) GLP-1 receptor agonists and cardiorenal outcomes in type 2 diabetes: an updated meta-analysis of eight CVOTs. Cardiovasc Diabetol 20(1):189. [34].

- An excellent overview of GLP-1 analog cardiovascular outcome trials.

Schlögl H, et al. (2013) Exenatide-induced reduction in energy intake is associated with increase in hypothalamic connectivity. Diabetes Care. 36(7):1933-40. [14].

- First neuroimaging study, which investigates the central nervous effects of GLP-1 analog administration in humans with functional MRI, demonstration changes of hypothalamic activity after GLP-1 analog administration, which are accompanied by decreased hunger and reduced energy intake.

Glossary

Glucagon-like peptide 1 (GLP-1) Peptide hormone produced mainly in the L-cells of the distal ileum and the colon. Increases insulin secretion of the **β**-cells of the pancreas when blood glucose is elevated. Analogs of GLP-1 were the first incretin mimetics approved for the treatment of type 2 diabetes.

Gastric inhibitory polypeptide (GIP, later also termed glucose-dependent insulinotropic peptide) Peptide hormone produced in the enteroendocrine cells of the duodenum and the jejunum. Increases insulin secretion of the **β**-cells of the pancreas when blood glucose is elevated.

Functional magnetic resonance imaging (fMRI) Technique to assess brain perfusion and thus receive information about the activity of different areas of the brain.

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Sodium-Glucose Cotransporter 2 Inhibitors

36

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Introduction

The concentration of glucose in plasma is held within narrow limits primarily to ensure fuel supply to the brain; the kidneys play a key role in glucose homeostasis by ensuring that glucose is not lost in the urine [1]. Contrary to common belief, the liver is not the only gluconeogenic organ although it does produce 80% of the endogenously derived glucose; the remaining 20% is produced by the kidney, which also contains the necessary gluconeogenic enzymes [2]. In non-diabetic individuals, the kidney filters approximately 180 mg of glucose daily [2]. Ninety percent of this is absorbed via the energy-dependent sodium-glucose cotransporter receptor moving from the tubular lumen to the arterioles via GLUT 4 glucose transport back into the circulation; the remaining 10% is reabsorbed in the distal collecting tubule leaving no glucose excreted into the urine [2]. Both at the liver and kidney, insulin is a potent inhibitor of gluconeogenesis; most of the filtered glucose is reabsorbed by the cotransporter enzyme SGLT2, and the remaining 10–20% is reabsorbed by the cotransporter SGLT1 [3]. Although the kidneys freely filter plasma glucose, none appears in the urine [1]. Glucose reabsorption from the glomerular filtrate by SGLT2 and SGLT1 occurs at different segments of the apical membrane of cells in the proximal tubule and from the passive exit of glucose through the basolateral membrane to the plasma via GLUT2, and at the expense of the extrusion of three sodium ions for every tw potassium ions entering the cell [1–3]. Glucose produced by renal gluconeogenesis is completely consumed by the kidney, but in patients with type 2 diabetes, insulin resistance increases the production of glucose in the kidney and liver despite high levels of fasting glucose [3].

One of the most important entries into the diabetes therapy armamentarium is the sodium-glucose cotransporter 2 inhibitors (SGLT 2 inhibitors), which first reached the US and European markets in early 2013. The idea for this mechanism of action is derived from the identification of an older drug, phlorizin, originally derived from the bark of an apple tree as a treatment for malaria [4]. Phlorizin caused marked increase in urinary glucose excretion through competitive inhibition of SGLT2, the principal transporter of renal glucose reabsorption and of SGLT1, a lesser glucose transporter in the kidney [3]. Phlorizin was useful for mechanistic studies in animal models but was too toxic for use in patients [5]. Additionally, there is a naturally occurring mutation in this co-transporter found in less than 1% of the population from the analysis of familial renal glucosuria, a rare genetic disorder of renal glucose transport [6, 7]. These patients have been known for decades since the original study of Hjärne of three generations of a single family [8, 9]. They have glucosuria with normal plasma glucose unless they also happen to have diabetes, which occurs rarely in this population. They seem to live perfectly normal lives except for increased risk of vaginal candidiasis related to glycosuria. Work began in the 1990s looking for less-toxic analogs of phlorizin, which led to the currently available marketed drugs with the discovery of dapagliflozin and canagliflozin [10, 11].

The Emergence of Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i)

These drugs have rapidly become extremely valuable tools in treating diabetes. Most of the published data has come from type 2 diabetes trials although in recent years an increasing number of studies about their use in type 1 diabetes have also been published. All the currently available SGLTi reduce both fasting and postprandial hyperglycemia and HbA1c between 0.6–1.0% [12–14]. There is also associated weight loss averaging 1–5 kg in most patients, presumably related primarily to caloric loss from excreted glucose [12]. The mechanism of action is independent of insulin itself and therefore should

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remain effective at all stages of the disease and work in a complementary fashion with other antidiabetics [12]. The risk of hypoglycemia with the use of SGLTi as monotherapy is similar to the use of other agents unless they are paired with sulfonylureas or insulin [15]. Several other interesting metabolic consequences have been identified including somewhat elevated plasma glucagon and ketone body production, which will be elaborated on further in this chapter, in addition to cardiorenal and pleiotropic effects [16–21].

As of December 2021, the FDA and European agencies have four agents for clinical use: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. Six additional compounds have undergone clinical trials: tofogliflozin [22], luseogliflozin [23], bexagliflozin [24], sotagliflozin [25], remogliflozin [26], ipragliflozin [27], and recent basic research that has confirmed the SGLT2 inhibitor properties of swertisin, a novel islet cell differentiation inducer [28, 29]. Table 36.1 shows the current list of SGLT2 inhibitors including FDA-approved and non-FDA approved.

The efficacy and safety data appear similar for the drugs studied to date, and very few head-to-head trials are available for direct comparison. The efficacy and side effects appear similar in most trials. In general, phase 3 trials have shown a HbA1c reduction of 0.7–1.0% as monotherapy or in addition to other antidiabetic agents including insulin.

Mechanism of Action

In diabetes, there is an apparently maladaptive *increase* in the tubular threshold from the normal of 180 mg up to 220–240 mg making it even harder to eliminate excess serum glu-

Table 36.1 SGLT Inhibitors

Name	Dosage	HbA1c reduction	Additional benefits	Comments
Canagliflozin	100, 300 mg/day	0.77–1.03%	Reduced risk of cardiovascular death, myocardial infarction or stroke (CANVAS) Blood pressure reduction	Risk of lower limb amputations
Empagliflozin	10, 25 mg/day	0.66–0.78%	Reduced risk of heart failure and cardiovascular death (EMPA-REG OUTCOME, RECEDE-CHF) Blood pressure reduction (EMPA-REG BP) Effective in patients with previous stroke or myocardial infarction	
Dapagliflozin	5, 10 mg/day	0.82–0.89%	Reduced risk of cardiovascular death and hospitalization from heart failure (DECLARE-TIMI) LDL cholesterol reduction	
Ertugliflozin	5, 15 mg/day	0.99–1.16%	In patients with chronic kidney disease stage 3A, reduce HbA1c, body weight, systolic blood pressure, maintaining glomerular filtration rate (VERTIS-CV)	Reduce dose in patients with glomerular filtration rate <60 mL/min/1.73 m^2
Tofogliflozin	5, 10, 20, 40 mg/day	0.56–0.68%	Post-marketing surveillance showed consistent reductions in HbA1c and body weight; 12.6% of patients reported adverse drug reactions (ADR), including serious ADR in 1.5% of patients	By comparison with other SGLT2 inhibitors, clinical and real-world studies remain sparse
Luseogliflozin[a]	2.5, 5 mg/day	0.37–0.60%	Significant decreases in HbA1c and body weight, especially in patients with higher body mass index	By comparison with other SGLT2 inhibitors, clinical and real-world studies remain sparse
Bexagliflozin[a]	5, 10, 20 mg/day	0.55–0.80%	Significant decreases in HbA1c, fasting blood glucose and body weight Similar incidence of adverse events in all active arms	By comparison with other SGLT2 inhibitors, clinical and real-world studies remain sparse
Sotagliflozin[a]	200, 400 mg/day	0.42%	Significant decreases in HbA1c, body weight and systolic blood pressure Reduced incidence of heart failure by 32%, myocardial infarction by 28%; neutral effects on all-cause mortality, cardiovascular mortality and stroke Reduced risk of cardiovascular death, emergency visits and hospitalization from heart failure (SCORED)	Increased incidence of diarrhea, genital mycotic infections, volume depletion and diabetic ketoacidosis
Ipragliflozin[a]	50 mg/day	0.24–1.30%	Significant decreases in HbA1c, fasting blood glucose (8.2–46.5 mg/dL), body weight and triglycerides	By comparison with placebo, no differences in blood pressure, low density lipoproteins or uric acid By comparison with other SGLT2 inhibitors, clinical and real-world studies remain sparse
Remogliflozin[a]	100, 250 mg/day	0.72%	Significant decrease in fasting and postprandial blood glucose: 17.8 mg/dL and 39.2 mg/dL respectively Overall incidence of adverse events: 8.5%, including genital mycotic and urinary tract infections; hypoglycemia incidence: 1.3%	By comparison with other SGLT2 inhibitors, clinical and real-world studies remain sparse

[a]Still not Approved by the FDA

cose. In the presence of SGLT 2 inhibitors, the threshold for glucose elimination is reduced to about 40 mg, allowing much more glucose loss. This tends to reduce both fasting and postprandial glucose levels [30]. As there is caloric loss from increased glucose excretion, weight loss is usually seen as well in the range of 2–3 kg in most studies. Approximately two thirds of the loss is secondary to fat loss and one third from fluid loss. A molecule of sodium is also excreted with each molecule of glucose resulting associated with a net loss of body sodium and to a small reduction in systolic blood pressure averaging about 5 mmHg. This may be beneficial since most patients tend to have some sodium excess. However, in patients somewhat sodium or volume depleted, this could result in excessive blood pressure reduction and dehydration. In the United States, the Food and Drug Administration (FDA) has reported approximately 100 cases of acute kidney injury to patients placed on these drugs. Many cases are seen in older patients with some renal dysfunction who are also taking loop diuretics. Therefore, cautious is advised in these patients, starting with lower doses and observing the initial response.

Individual Profiles

Canagliflozin was approved by the FDA in the United States in March of 2013 for use in patients with type 2 diabetes mellitus, and it was the first of the SGLT2 inhibitors to be released in the market. The initial dose is 100 mg daily and can be increased to 300 mg in those tolerating the medication if GFR is ≥60 mL/min/1.73 m^2. Fixed doses of canagliflozin in combination with metformin are available in 50/500, 50/1000, 150/500, and 150/1000 mg [31]. Glucosuric effects are estimated to be an excretion of approximately 100 g of urinary glucose per day. It has the most largest glucosuric effect among approved SGLT2 inhibitors. In addition to its main effect as an SGLT2 inhibitor, canagliflozin induces weak inhibition of SGLT1, which is located in both the gut and renal tubules. SGLT1 inhibition is thought to have effects in lowering postprandial hyperglycemia by delaying intestinal glucose absorption, an observation from studies published in 2013 [32].

Comparative Efficacy and Safety of Canagliflozin with Oral Antidiabetics

The efficacy of canagliflozin has been studied as add-on therapy to metformin in comparison with other antihyperglycemic agents such as DPP4-inhibtors and sulfonylureas according to a randomized, double blinded trial was published in 2013 comparing the efficacy of canagliflozin with sitagliptin in patients on monotherapy with metformin ≥1500 mg daily. After 52 weeks, both sitagliptin 100 mg and canagliflozin 100 mg were effective in lowering HbA1C by an average of 0.73%, while canagliflozin at a dose of 300 mg/day decreased HbA1C by 0.88% [33]. Both canagliflozin doses were superior in weight reduction (3.8% and 4.2%) compared with a decrease of 1.3% in the sitagliptin group [33].

In 2015, canagliflozin was compared with glimepiride in a phase 3, randomized, double blinded, 104 week-long study as add-on therapy for diabetic patients already on therapeutic doses (≥1500 mg today daily) of metformin [34]. Canagliflozin decreased HbA1C by an average of 0.65% for the 100 mg dose and 0.74% for the 300 mg dose in comparison to glimepiride, which resulted in an average 0.55% reduction. The use of canagliflozin was associated with a lower risk of hypoglycemia, with a prevalence of 40% in the glimepiride group and only 6 and 8% in the canagliflozin 100 mg and 300 mg groups, respectively. Weight loss was observed with canagliflozin, as opposed to weight gain for patients on glimepiride, with an average loss of 4.1% (3.6 kg) of pretreatment body weight for the 100 mg and 4.2% (3.6 kg) for the 300 mg groups [34].

Comparative Efficacy of Canagliflozin with Insulin

Data about the use of canagliflozin in patients on insulin therapy were published in one of the reports of the CANVAS trial comparing canagliflozin and placebo to patients on basal or basal-bolus insulin for 18 weeks with a 52-week follow-up [35]. The addition of canagliflozin to insulin improved glycemic control: HbA1c was 8.3% in both groups; at 18 weeks, reductions in HbA1c of 0.62% and 0.73% for canagliflozin 100 mg and 300 mg, respectively, were observed in comparison to placebo with persisting differences in HbA1c after 52 weeks with a reduction of 0.58% in the 100 mg group and 0.73% in the 300 mg group in comparison to placebo [35]. There were differences in weight and blood pressure reduction as well. A weight loss of 1.9% and 2.4% was seen for each canagliflozin dose. Systolic blood pressure decreased by an average of 3.1 and 6.2 mmHg and diastolic blood pressure by 1.2 and 2.4 mmHg in each of the canagliflozin groups [35]. In another randomized controlled trial, the efficacy and safety of canagliflozin was compared with liraglutide in patients with type 2 diabetes previously controlled with multiple doses of insulin (MDD) [36]. Basal insulin was maintained, and bolus insulin was randomly switched to canagliflozin, 100 mg/day or liraglutide, 0.30.3–0.9 mg/day for 24 weeks [36]. Changes in HbA1c were comparable between treatments, and both treatments maintained HbA1c levels as baseline with stable glucose variability and no severe hypoglycemia at 24 weeks, with reduced total insulin doses and improvements in quality of life [36].

Safety and efficacy of canagliflozin has been evaluated in patients with preexisting chronic kidney disease with GFRs between ≥30 and ≤50 mL/min/1.73 m^2. Placebo-subtracted differences in A1c values were seen for the 100 mg and 300 mg groups from baseline (0.27% and 0.41%). Lower body weight and blood pressure for both doses in comparison with placebo were also documented [37].

Dapagliflozin was approved for treatment in patients with type 2 diabetes mellitus in the United States in 2014 as an adjunct to diet and exercise. It is a highly selective SGLT2 inhibitor. The initial dose is 5 mg, which can be increased to 10 mg orally daily. It is available in combination with metformin as well [31].

Dapagliflozin has been observed to be non-inferior to sulfonylureas and superior to DPP-4 inhibitors as add-on therapy to metformin. Monotherapy comparing metformin and dapagliflozin has been evaluated in treatment naïve patients. Results from this study demonstrated non-inferiority between metformin and dapagliflozin. Dapagliflozin as monotherapy decreased HbA1C by an average range of 0.55–0.9% in comparison to 0.73% with metformin [38]. Dapagliflozin is also effective in lowering HbA1c when added to metformin. A 52-week double-blinded trial with patients having HbA1c values between 8% and 12% at baseline showed significant improvement [39]. Dapagliflozin added to metformin decreased HbA1C an average of 1.2%, which was significantly lower than the combination of saxagliptin with metformin (0.9%). This study also compared triple therapy with all three agents and found superiority to dual therapy by reducing HbA1c by up to 1.5%. Weight loss was superior in the dual therapy dapagliflozin and metformin group with an average loss of 2.8% (2.1 kg) and in the triple therapy group, which lost an average of 2.4% (2.1 kg) compared to the saxagliptin and metformin group (no significant change seen) [39]. The efficacy of dapagliflozin has been compared to sulfonylureas: glipizide was compared to dapagliflozin and resulted in non-inferiority at 52 weeks [40]. This trial was extended for 2 years, and a sustained decrement in HbA1C was observed with dapagliflozin compared with glipizide (0.32% vs 0.14%) [40]. An additional 52-week, randomized trial compared the efficacy and safety of dapagliflozin as monotherapy or combined with saxagliptin versus glimepiride in patients with type 2 diabetes previously receiving metformin [41]. Mean HbA1c change from baseline was −0.82 with dapagliflozin alone, −1.20% with dapagliflozin plus saxagliptin, and −0.99% with glimepiride [49]. Fasting blood glucose decreased significantly with dapagliflozin plus saxagliptin compared with glimepiride and was similar when not in combination [41]. Both dapagliflozin regimens decreased body weight and systolic blood pressure; the combined incidence of hypoglycemia was lower with dapagliflozin, and genital infections were more frequent [41].

Empagliflozin the FDA-approved empagliflozin as an antihyperglycemic agent to be used in patients with type 2 diabetes mellitus in the United States in 2014. It is available in a starting dose of 10 mg, which can be increased to 25 mg daily in patients with a GFR ≥ 45 mL/min/1.73 m^2. Its glucosuric effects are estimated to be 78 g of glucose per day. Like canagliflozin and dapagliflozin, it also has weight loss and blood pressure-lowering effects.

Empagliflozin has been studied as add-on therapy to metformin in comparison to sulfonylureas as well as triple therapy with DPP-4 inhibitors and metformin. A double -phase 3, 104-week long study in patients with poor diabetes control on monotherapy with metformin was randomized to either glimepiride or empagliflozin therapy [42]. At baseline HbA1c levels between 7% and 10%, empagliflozin 25 mg significantly decreased HbA1c a mean of 0.11% more than glimepiride. Adverse events were similar in both groups, but there was a marked difference in the frequency of hypoglycemia between the empagliflozin and glimepiride groups (2% vs 24%) [42]. A 208-week extension of this trial, the adjusted mean difference in change from baseline in HbA1c with empagliflozin versus glimepiride, was statistically significant, and hypoglycemic episodes occurred in 3% of patients on empagliflozin and 28% on patients receiving glimepiride [43]. Addition of empagliflozin 10 mg and 25 mg was compared to placebo in a 24-week long, double-blinded trial with poorly controlled type 2 diabetic patients on linagliptin and metformin combination therapy [44]. By comparison with placebo, the empagliflozin 10 mg and 25 mg groups were observed to have a −0.79% and −0.7% difference in HbA1c from baseline. Addition of empagliflozin to linagliptin and metformin had no added adverse effects. Weight loss and blood pressure benefits were seen in both empagliflozin groups. Hypoglycemia occurred more frequently in the empagliflozin 25 mg group versus the placebo group in this trial (2.7% vs 0.9%) [44]. Positive outcomes and improvement in glycemic control have been observed with the use of empagliflozin with other agents including sitagliptin, pioglitazone, and insulin therapy (both basal and basal/bolus regimens) [45–48]. Recent comparisons between 25 mg empagliflozin and one-weekly 1 mg oral semaglutide have shown significant differences on HbA1c and body weight versus empagliflozin [49, 50].

Cardiovascular Benefits of SGLT2 Inhibitors

Approvals for most new antidiabetic agents in the United States have included a requirement for generally large-scale cardiovascular outcome trials primarily to be certain they do not increase cardiovascular risk. The first of these for this new class was presented at the European Association for the Study of Diabetes (EASD) in September 2015. In contrast to previous studies, this one for empagliflozin (EMPA-REG Trial) showed striking benefit particularly in cardiovascular mortality (38% relative risk reduction), hospitalizations for congestive heart failure (35% relative risk reduction), and death from any cause (32% relative risk reduction). Death from any cause was reduced by 32% [51]. This was much less striking for myocardial infarctions and nonexistent for stroke benefit. The median duration of this trial was 3.1 years. Remarkably, the survival curves began to diverge within about 3 months of beginning the trial. Although there was an expected reduction in plasma glucose, it seems unlikely that this effect could result in a benefit of this magnitude so quickly. A proposed mechanism for such rapid benefits has been reduction in arterial stiffness. Sodium and glucose loss reduces extracellular fluid volume and blood pressure. This reduces car-

diac pre and after load and myocardial metabolism, improving both systolic and diastolic function. All of this may play a role in the observed rapid reduction in hospitalizations for heart failure and cardiac death. The majority of subjects were treated with platelet inhibitors, statins, and adequate blood pressure control. Therefore, the benefits appear to be over and above these standard therapies [52]. In addition to their established efficacy as antidiabetics, clinical trials comparing the use of empagliflozin with GLP-1 agonists have shown that the use of SGLT2 inhibitors is associated with consistent reductions in hospitalization for heart failure among type 2 patients with and without cardiovascular disease (CVD), although the absolute reduction is greater in patients with CVD (Fig. 36.1) [53].

What could account for these remarkable improvements? The known effects of the drug are unlikely to account for the magnitude of this effect. Reduction in arterial stiffness had been observed with these drugs verified by arterial ultrasound compression [54]. The onset of heart failure sets in motion a cascade of effects, which may lead to a vicious cycle of vasoconstriction with activation of the adrenergic nervous system and the renin-angiotensin-aldosterone system including the tubular glomerular feedback in the kidney, which may alter this adverse sequence of events. The sum total of these changes likely reduce cardiac preload and afterload and improve myocardial oxygen supply [55].

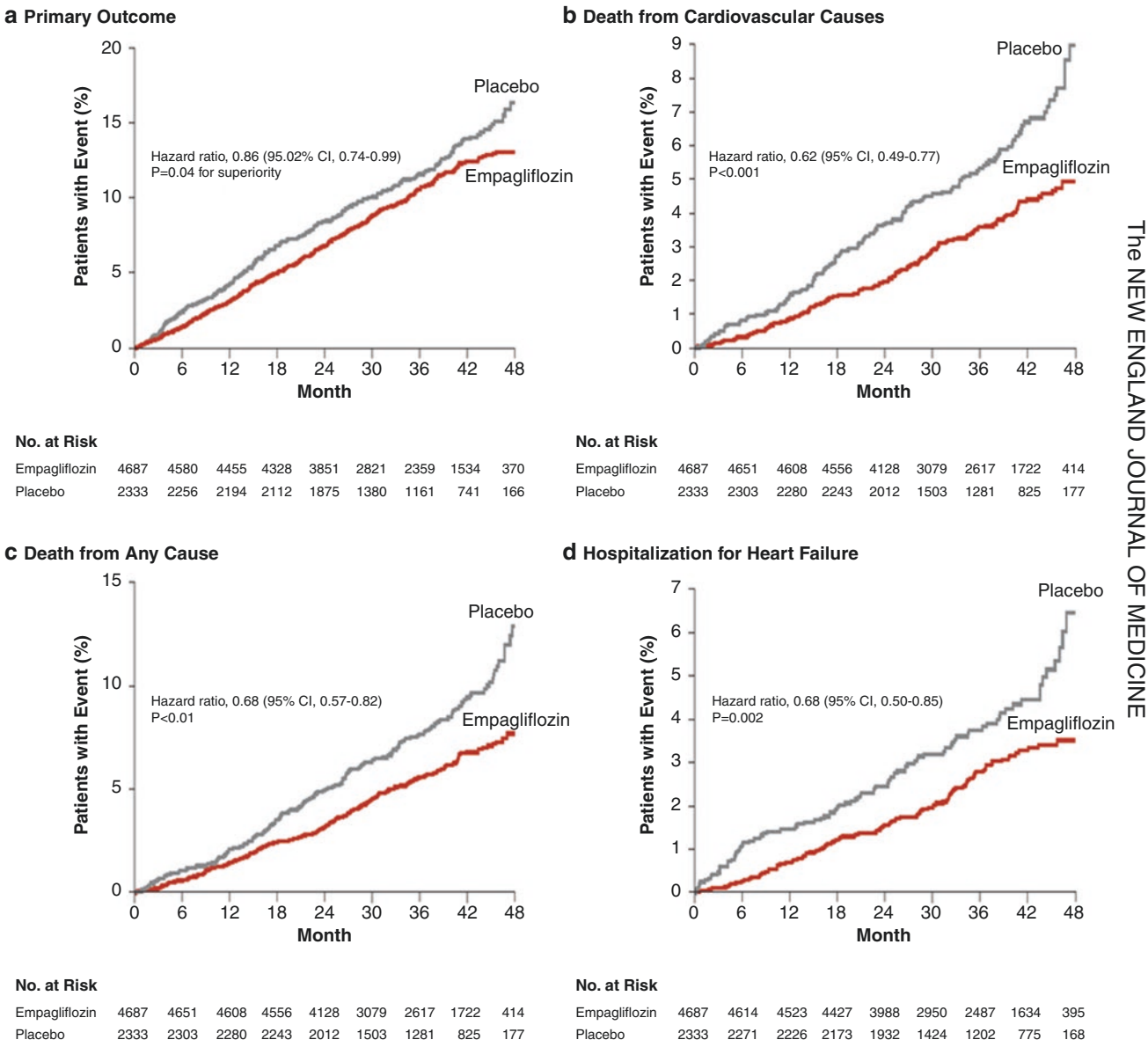


Fig. 36.1 Cardiovascular outcomes and death from any cause. Shown are the cumulative incidence of the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel **a**), cumulative incidence of death from cardiovascular causes (Panel **b**), the Kaplan–Meier estimate for death from any cause (Panel **c**), and the cumulative incidence of hospitalization for heart failure (Panel **d**) in the pooled empagliflozin group and the placebo group among patients who received at least one dose of a study drug. Hazard ratios are based on Cox regression analyses (Zinman NEJM 2015)

The first report of the results of the cardiovascular and renal outcomes CANVAS trial for canagliflozin was published in 2017 [56]. The rate of the primary outcome, a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke was lower with canagliflozin than with placebo, occurring in 26.9% versus 31.5 participants ($P < 0.001$) [56]. Renal outcomes were not statistically significant, but the results showed possible benefits of canagliflozin on the progression of albuminuria and the composite outcome of a sustained reduction in glomerular filtration rate, the need for renal replacement therapy, or death from renal causes. Adverse reactions showed and increased risk for amputations at the level of toe or metatarsal [56]. The first report of the DECLARE-TIMI 58 dapagliflozin cardiovascular outcome trial was published in 2019 [57]. In the primary safety analysis, dapagliflozin met the prespecified criterion for noninferiority to placebo with respect to major adverse cardiovascular events (MACE) defined by cardiovascular death, myocardial infarction, or ischemic stroke. Patients in the dapagliflozin group had lower rates of cardiovascular death or hospitalization for heart failure, without between-group difference in cardiovascular death [57]. Diabetic ketoacidosis was more common with dapagliflozin than with placebo (0.3% vs 0.1%) as was the rate of genital infections leading to discontinuation (0.9% vs 0.1%) [57]. The first report to assess cardiovascular outcomes with ertugliflozin from the VERTIS CV trial showed equal rates of major cardiovascular events (11.9%) in the ertugliflozin group and with placebo [58]. Death from cardiovascular causes or hospitalization for heart failure occurred in 8.1% of patients in the ertugliflozin group and 9.1% of patients in the placebo group, and the hazard ratio for death from cardiovascular causes was 0.92 [58]. Amputations were performed in 2.0% of patients who received the 2 mg dose and 2.1% of patients who received the 15 mg dose, as compared with 1.6% of patients who received placebo [58].

Renal Effects

Renoprotective effects of SGLT2 inhibitors were also analyzed in the EMPA-REG, CANVAS, DECLARE-TIMI 58, and VERTIS trials [53, 56–59]. In a subsequent preplanned sub-study (EMPA_REG Renal), significant benefits were observed in those having renal dysfunction with estimated glomerular filtration rates (GFR) of 30–60 mL/min [59]. There is a transient small drop in GFR seen on initiating these drugs that is possibly related to diuresis and volume contraction. However, as can be readily seen from Figs. 36.2 and 36.3, the net result was positive for preservation of renal function com-

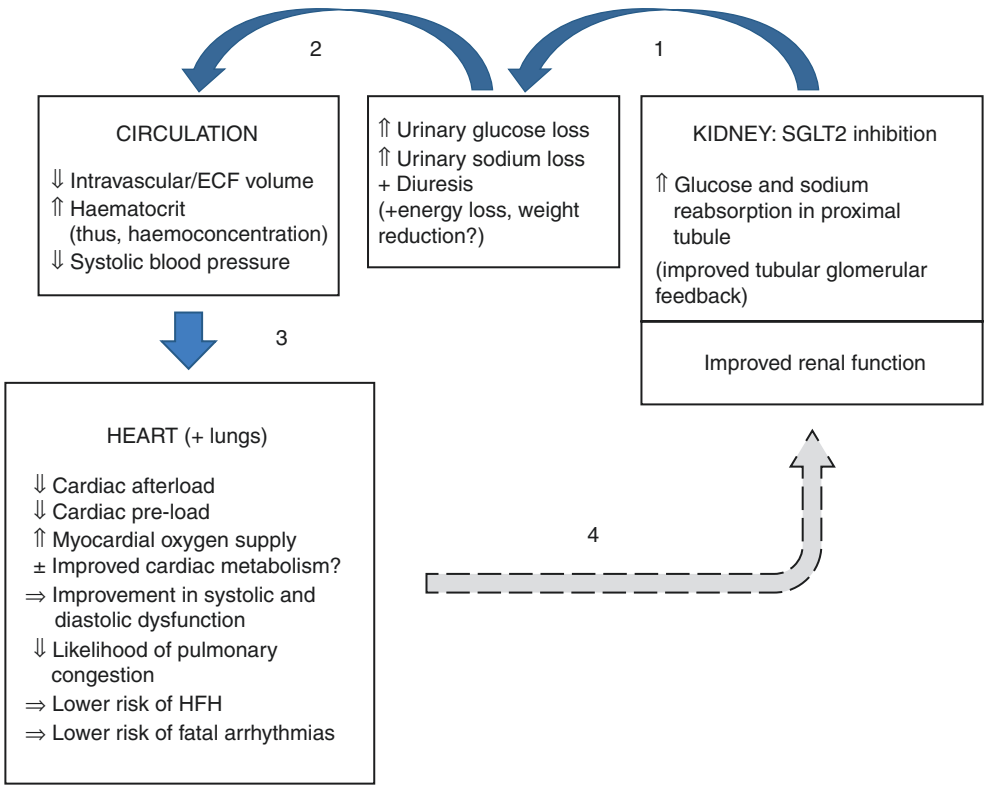


Fig. 36.2 Potential pathway linking empagliflozin (and possibly other SGLT2 inhibitors) with lower risks for HFH (and, linked to this, death due to cardiovascular disease). By increasing fluid losses via urinary glucose and sodium losses (1), intravascular volumes and systolic blood pressure are reduced and there is a significant rise in hematocrit (2). These latter effects may also be, to a small extent, assisted by weight loss. These changes in turn lessen cardiac stressors (pre- and afterload) and may also help improve myocardial oxygen supply (3). The net result is a likely improvement in cardiac systolic and diastolic function, lessening chances of pulmonary congestion, thus lowering risks of HFH and fatal arrhythmias. These cardiac function benefits will, in turn, feed back to improve renal blood flow and function (4). In this way, the cardio-renal axis is improved at a number of levels with SGLT2 inhibitor therapy (Sattar dibetologia 2016)

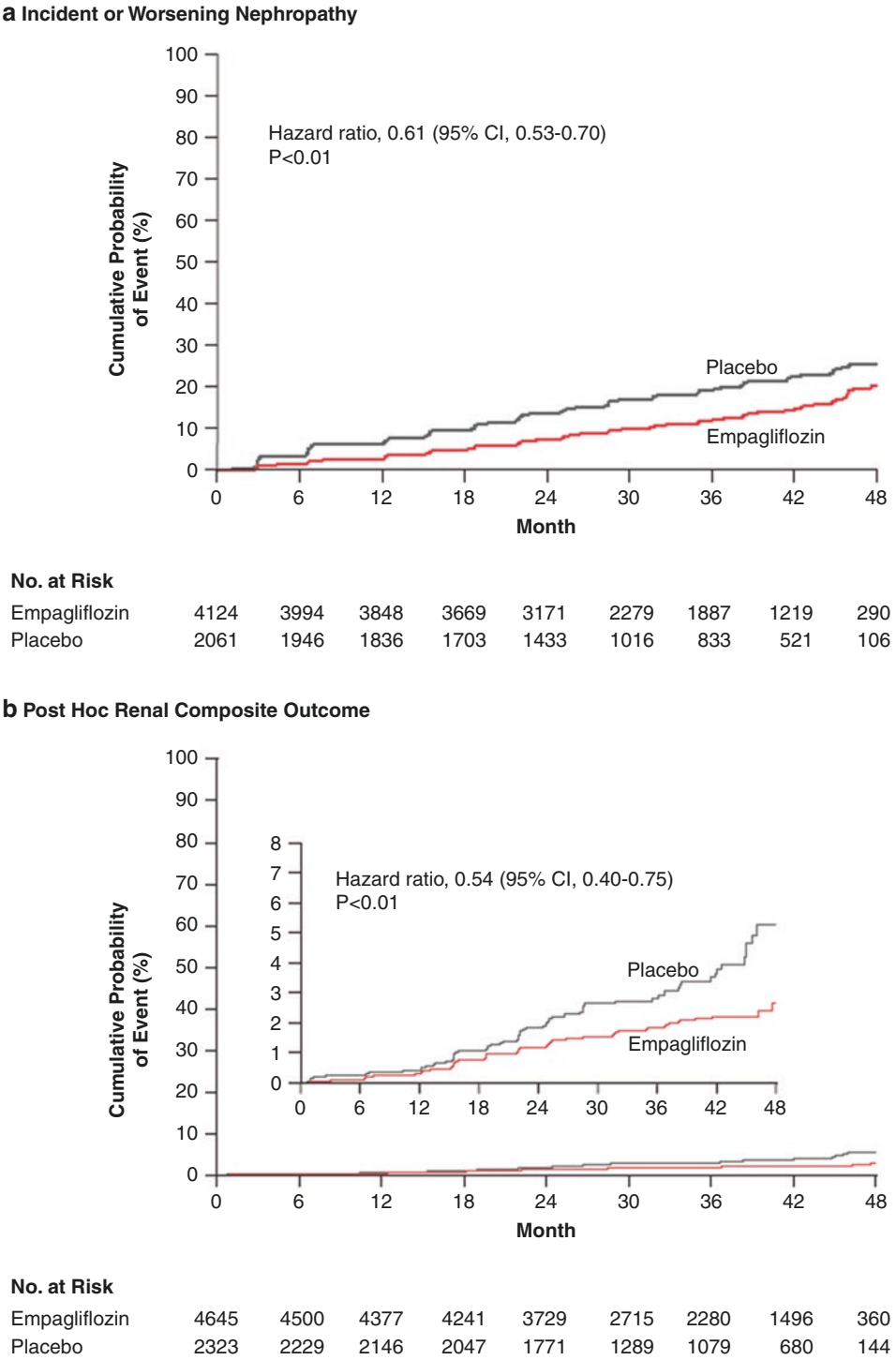
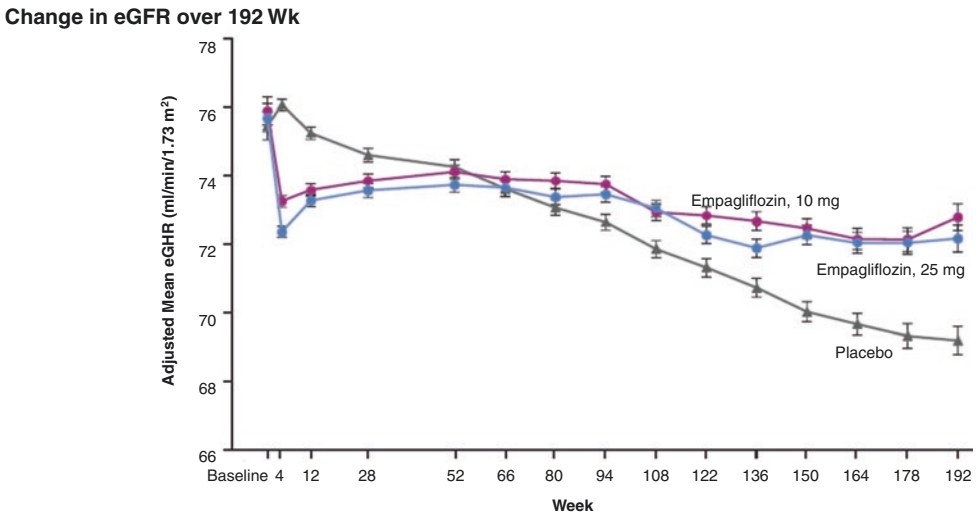


Fig. 36.3 Kaplan–Meier analysis of two key renal outcomes. Shown are estimates of the probability of a first occurrence of a prespecified real composite outcome of incident or worsening nephropathy (Panel a) and of a post hoc renal composite outcome (a doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal failure (Wanner NEJM 2016 panel **a** & **b** and Panel **a**)

Fig. 36.3 (continued)



No. at Risk															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin, 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in Follow-up Analysis															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

pared to the placebo treated arm in which there was small continuing loss of eGFR. Renal endpoints of newly appearing or worsening nephropathy and progression to macroalbuminuria were reduced by 29% and 38%, respectively. Hard renal endpoints of doubling of serum creatinine and need for renal replacement were reduced by 44% and 55%, respectively, although the latter endpoint occurred in relatively few subjects. These subjects were treated with standard of care with 79–85% receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Therefore, the benefits are additive and over and above those seen with treatments known to be effective [59]. A recent sub-analysis from the VERTIS trial in patients with an estimated glomerular filtration rate (GFR) 30 to < 60 mL/min showed that in addition to reduction in HbA1c, body weight, and blood pressure, patients receiving ertugliflozin maintained baseline GFR levels [60]. The prospect of significantly reducing the decline of GFR in chronic diabetic chronic kidney disease is exciting [61].

The Canagliflozin and Renal Events in Diabetes and Established Clinical Evaluation (CREDENCE) compared canagliflozin versus placebo in patients with type 2 diabetes and chronic kidney disease [62]. Canagliflozin significantly reduced the risk of the primary composite outcome: end-stage renal disease, doubling of serum creatinine, renal, or cardiovascular death. The CREDENCE trial was stopped early for efficacy after an interim analysis and recommendation from the independent Data Monitoring Committee [63]. Overall, the results of the CREDENCE trial showed that canagliflozin could be safely administered to patients with diabetic nephropathy, despite an initial drop in glomerular filtration rate. Ongoing kidney disease-focused outcome trials including DAPA-CKD and EMPA-KIDNEY will provide further information about the use of SGLT2 inhibitors in patients with type 2 diabetes and different stages of chronic kidney disease [64].

Other Metabolic Effects: Increased Ketogenesis a "Superfuel?"

SGLT2 inhibitors are known to increase glucagon, beta-hydroxybutyrate, and ketone body production. In this sense, they appear to shift metabolism from glucose to fat oxidation. Ketone bodies are readily taken up by the myocardial cells as fuel. Myocardium has the highest myocardial oxygen consumption at 8 mL O_2/100 g of tissue followed by 5 mL O_2 for kidney and 3 mL for brain tissue. It is postulated that an increased availability and use of ketone bodies could be beneficial to metabolically stressed organs [65, 66]. There is experimental evidence that this may result in more efficient oxygen sparing and cardiac work for any given level of demand. This could provide another mechanism for more rapid cardiac benefit in addition to a variety of potential pleiotropic effects beyond glucose lowering on a variety of diseases, including nonalcoholic fatty liver disease and obesity [14, 21].

Safety and Tolerability

SGLT2 are safe and well tolerated [12]. Rates of discontinuation in clinical trials are low, but according to their mechanism of action, they cause osmotic diuresis, volume depletion, and dehydration [12, 14]. Patients at risk, including those with frailty, the elderly, or taking diuretics, should be monitored and advised about these effects.

Genitourinary Infections

The most common adverse events is a higher risk for lower urinary tract infections, vulvovaginitis and vaginitis of bacterial and mycotic origin, which was documented in clinical trials and case reports [12, 14, 16]. A study by Lega et al. reported a five times higher risk of genital mycotic infections in patients treated with SGLT2 inhibitors, increasing in the first month of therapy and enduring for the duration of treatment [67]. Glycosuria resulting from diabetes provides a favorable substrate for microorganism growth, which is enhanced by the pharmacologic glycosuria induced by SGLT2 inhibitors [68]. Incidence rates of mycotic genital infections in clinical trials are 6.0% and more common in women [68]. The incidence of bacterial infections ranges from 4.0% to 9.0%, while severe infections occur in 0.4% of patients [68]. Severe forms of genitourinary infections include pyelonephritis, emphysematous pyelonephritis, and Fournier gangrene, a perineal disease of acute onset and rapid progression [69].

Ketoacidosis

There has been concern about increased ketone body production particularly in very insulin-deficient patents such as type 1 diabetics. There are several case series raising this concern of ketoacidosis. The rate appears to be low in type 2 diabetes. The mechanism of action could be related to decreased insulin levels, which leads to unopposed glucagon production and lipolysis, which leads to ketogenesis. Risk factors and precipitants for diabetic ketoacidosis related to SGLT-2 inhibitors are sepsis, dehydration, surgeries, decrease in insulin dose administration (for those on insulin), and a low carbohydrate diet [69]. The risk of ketoacidosis could be minimized by educating all patients upon initiation of therapy that nausea, vomiting, and dehydration require checking for ketones, and such symptoms should prompt them to seek medical attention [70].

Additional side effects include amputations and bone fractures.

Conclusion

SGLT-2 inhibitors are the newest pharmacologic resource for management of type 2 diabetes. Since their approval and release into the market in the United States in 2013, multiple studies have proven both efficacy and positive cardiovascular and renal outcomes. Their use has also enhanced our knowledge on fuel metabolism and the use of ketones as a source of energy. Although generally well tolerated, clinicians should be on alert for possible adverse effects of dehydration and even normoglycemic diabetic ketoacidosis. The use of these agents is expected to rise given their marked improvements in HbA1c in addition to beneficial effects on weight, blood pressure, and cardiovascular outcomes.

Multiple Choice Questions

1. In patients with diabetes, the tubular threshold for the excretion of glucose:
   (a) Is decreased
   (b) Is adapted and increased
   (c) **Is maladapted and increased**
   (d) Is not different from people without diabetes
   (e) Is able to eliminate excess serum glucose
2. In the presence of SGLT 2 inhibitors, the threshold for glucose elimination is reduced:
   (a) Approximately 10 mg
   (b) Approximately 20 mg
   (c) **Approximately 40 mg**
   (d) Approximately 80 mg
   (e) Approximately 100 mg
3. Weight loss with the use of SGLT 2 inhibitors is estimated in the range of:
   (a) 1–3 kg
   (b) **2–3 kg**
   (c) 3–4 kg
   (d) 4–5 kg
   (e) 5–6 kg
4. Weight loss from the use of SGLT 2 inhibitors is secondary:
   (a) **To fat loss**
   (b) To muscle loss
   (c) **To fluid loss**
   (d) All of the above
   (e) None of the above
5. Inhibition of SGLT 1, located in the gut and renal tubules, results in:
   (a) **Lowering postprandial hyperglycemia**
   (b) Lowering fasting blood glucose

(c) Lowering blood pressure
(d) Increasing glucose uptake
(e) Increasing intestinal glucose absorption

6. Range doses of canagliflozin:
   (a) 5–10 mg daily
   (b) 10–25 mg daily
   (c) 50–100 mg daily
   (d) **100–300 mg daily**
   (e) 150–200 mg daily
7. Range doses of dapagliflozin:
   (a) **5–10 mg daily**
   (b) 10–25 mg daily
   (c) 50–100 mg daily
   (d) 100–300 mg daily
   (e) 150–200 mg daily
8. Range doses of empagliflozin:
   (a) 5–10 mg daily
   (b) **10–25 mg daily**
   (c) 50–100 mg daily
   (d) 100–300 mg daily
   (e) 150–200 mg daily
9. The results of the EMPA-REG Trial showed that the use of empagliflozin was associated:
   (a) With a 38% relative risk reduction in cardiovascular mortality
   (b) With a 35% relative risk reduction for congestive heart failure
   (c) With a 32% relative risk reduction of death from any cause
   (d) **All of the above**
   (e) None of the above
10. Cardiovascular benefits from the use of SGLT 2 inhibitors have been attributed to:
   (a) The effect of additional medications standard cardiovascular therapies
   (b) **Reduction in arterial stiffness**
   (c) Regression of atherosclerotic plaques
   (d) Their anti-hypertensive effects
   (e) Inhibition synthesis of advanced glycation products (AGEs)

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Use of Insulin in Outpatient Diabetes Management

37

Raquel N. Faradji, Elena Sainz de la Maza, Ana Paula Díaz Barriga Menchaca, and Juan Ramón Madrigal Sanromán

Objectives

To know:

- The indications for insulin use
- The different insulin types and action times
- The different insulin regimens
  - How to initiate
  - How to adjust
- The insulin adverse effects
- The insulin storage and injection recommendations

Introduction

As time passes, clinical practice addresses a greater number of patients with diabetes, and the available drugs for diabetes treatment increase. Insulin is one of the most potent drugs for glucose control. Insulin therapy is a must for all patients with type 1 diabetes (T1D) and those patients with type 2 diabetes (T2D) who do not achieve their goals in glycemic control with antidiabetic oral or other injectable agents. It can be used from T2D diagnosis, in later stages of the disease, or at times of diabetes decompensation.

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Understanding insulin management is vital for every physician that treats diabetes and for every patient that lives with diabetes. The best treatment is the one that tends to be most similar to the physiologic secretion of insulin in the pancreas. This pattern has a peak in insulin secretion stimulated by meals and a basal secretion throughout the rest of the day. Basal insulin secretion is necessary for maintaining optimal glucose regulation in liver, muscle, and adipose tissue. Basal insulin is essential for modulating glucose production from the liver. The insulin peak after meals stimulates glucose uptake by tissues and stops endogenous production [1].

If there is an absolute insulin deficiency (T1D), a physiological secretion of insulin should be imitated with a multiple daily injection regimen, preferably in a basal-bolus manner.

If there is a relative insulin deficiency (T2D), insulin could be indicated to treat the hyperglycemia that occurs at certain times of the day, for example, at dawn, when elevation of cortisol levels leads to an increase in hepatic glucose production. Increase in glucose levels at dawn can be an important cause for basal insulin initiation in T2D patients. Oral medications help stimulate the secretion of endogenous insulin (sulfonylureas, glucagon-like peptide-1 receptor agonist-GLP-1ra, dipeptidyl peptidase-4-DPP-4 inhibitors) and cover the prandial requirements. When oral drugs fail, prandial insulin therapy may be added to meals where glucose levels are elevated (basal-plus) or at every meal (basal-bolus). In the latter case, metformin is usually continued, but sulfonylureas are suspended. It must be pointed out that before adding prandial insulin, one could add a GLP-1ra. In the author's experience, the combination of metformin with DPP-4 inhibitors or GLP-1ra and basal insulin can be very useful in many patients with low insulin requirements and can provide sustained glycemic control for a long time.

Insulin therapy should always be individualized. The aim is to improve glycemic control of patients living with diabetes. Glycemic control is normally measured through glycosylated hemoglobin A1c levels, pre-prandial glucose levels, and 2 h postprandial glucose levels, based on self-

J. Rodriguez-Saldana (ed.), *The Diabetes Textbook*, https://doi.org/10.1007/978-3-031-25519-9_37

Table 37.1 Glycemic targets

	Fasting glucose (mg/dL)	Postprandial glucose (mg/dL)	HbA1c %	TIR (70–180 mg/dL) %
No diabetes	70–99	≤139	≤5.6	>95
Adults (AACE)	<110	≤140	≤6.5	>70
Adults (ADA)	80–130	≤180	≤7.0	>70
Older adults (low risk)	90–130	≤180	≤7.5	>70
Older adultos (high riesgo)	100–180	<200	≤8.5	>50
Children/adolescents	70–130	90–180	<7.0	>70
Pregnancy	63–99	100–129	<6.0	>70 (63–140 mg/dL)

Based on Battelino T et al. 2019 [2], American Diabetes Association 2022 [3], AACE 2020 [4], ISPAD 2018 [29]

monitoring of blood glucose (SMBG) and recently time in range (TIR) based on continuous glucose monitoring (CGM) (Table 37.1). The goal is to have >70% time in range (70–180 mg/dL/3.9–10 mmol/L) and with the least glycemic variability (coefficient of variability less than 36%) [2]. An adequate glycemic control will help decrease the incidence of diabetes complications, which are a severe public health problem.

According to the degree of glycemic control, insulin can be administered with a simple regimen (basal insulin with nocturnal dosage of intermediate-acting (NPH) or a long or ultra-long-acting insulin analogue plus oral antidiabetics or other injectable drugs) or a more complex regimen (multiple daily injection regimen with NPH and regular or fast-acting insulin analogue twice a day, premixed insulin twice a day, basal-plus prandial or basal-plus GLP-1ra or a basal-bolus regimen).

Hypoglycemia is the main adverse effect of insulin use. Self-management education and self-monitoring and recording of blood glucose are vital to adjust insulin dosages and decrease the risk of hypoglycemia.

Patient Selection

Indications for insulin use are:

1. Patients with T1D, due to absolute insulin deficiency (if insulin is stopped, they could develop diabetic ketoacidosis).
2. Patients with T2D. They initially have an insulin resistance predominance: however, over time, they lose the ability to secrete insulin, which leads to different insulin deficiency/insulin resistance states, having different requirements according to progress in the natural history of the disease.

   Insulin is indicated in patients with type 2 diabetes (T2D):

   (a) Newly diagnosed patients who are very symptomatic, or in catabolic state with random hyperglycemia (>200 mg/dL or 11.1 mmol/L) and glycosylated hemoglobin A1c (A1c) > 9% or >75 mmol/mol.

   (b) Newly diagnosed patients in whom there is doubt as to whether they have T1D, T2D, or latent autoimmune diabetes in adults (LADA).

   (c) Patients who fail to obtain good glycemic control with oral antidiabetics (3 or more) or GLP-1ra at maximum tolerated doses, despite time of diagnosis.

   (d) Patients who have transient moderate to severe worsening of glycemic control such as in the case of surgery, pneumonia or any infection, acute myocardial infarction, hospitalization, use of glucocorticoids, etc.

   (e) Patients with diabetes who start with insulin from diagnosis to decrease the glucotoxicity and lipotoxicity in order to favor the rest of the insulin-producing beta cell and to try to preserve its function. It is well known that timely insulinization could restore beta cell function in type 2 diabetes.

   (f) Patients who have progression of chronic diabetes microvascular complications. Insulin is used to try to avoid further progression.
3. Pregnancy. Pregnant patients with previous diagnosis of diabetes and patients with gestational diabetes. Detemir and aspart insulin analogues are FDA approved for its use in pregnancy; however, NPH and regular insulin have traditionally been used. Although glargine and lispro insulin have been used safely during pregnancy, they are not FDA approved for its use.

Clinical Guidelines

Many guidelines and algorithms for T2D treatment have appeared in recent years [3, 4]. In general, all guidelines are based on trying to reach glycemic levels closest to normal while trying to avoid hypoglycemia. The goals for each patient with T2D should be individualized, and when glycemic control is not reached, treatment with oral antidiabetics should be scaled. Before choosing an antidiabetic drug, it is indicated to assess the risk of cardiovascular disease, one usually starts with monotherapy, and guidelines recommend to initiate an SGLT2 inhibition and/or GLP-1 receptor ago-

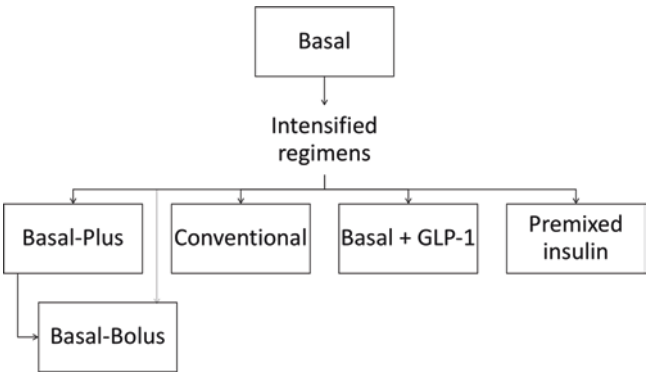

Fig. 37.1 Intensification of insulin regimens

nist with demonstrated cardiovascular disease benefit; otherwise, metformin is always indicated. If the A1c goal is not reached after 3 months, the treatment is scaled to dual therapy, and again if the A1c goal is not reached after 3 months, it can be scaled to triple therapy. In most guidelines [3, 4], basal insulin initiation is considered as an option at dual or triple therapy, although one must take into account the risk of hypoglycemia. If with triple therapy the goal is still not reached, then basal insulin therapy or intensification to combination injectable therapy should be considered. Combination injectable therapy includes basal-plus prandial insulin, basal plus GLP1-ra, basal-bolus, and the conventional regimen. If insulin is used, combination therapy with a GLP-1ra is recommended for greater efficacy and durability of treatment effect (Fig. 37.1).

The early introduction of insulin should be considered. If the patient is symptomatic, catabolic, with glycemia above 200 mg/dL (11.1 mmol/L), and/or A1c greater than 9 or 10%, then insulin should be started from the beginning.

The 2022 American Diabetes Association guidelines [3] point out that:

- The progressive nature of T2D should be regularly and objectively explained to the patients.
- It should be avoided to use insulin as a threat, describing it as a failure or punishment.
- In patients who are not achieving glycemic goals, insulin therapy should be promptly initiated.
- It is important for the patient to have a self-titration algorithm, based on SMBG.
- People who are on insulin using blood glucose monitoring should be encouraged to check when appropriate based on the insulin regimen (this includes fasting, prior to meals and snacks, at bedtime, prior to exercise, etc.)
- Continuous monitoring glucose (CGM) should be offered for diabetes management in people with diabetes on multiple daily injections (MDI) or CSII who are capable of using devices safely.

Insulin Types and Time of Action (Table 37.2 and Fig. 37.2)

Insulin is a molecule formed by two peptidic chains (α and β) linked by two disulfide bridges. The insulin currently available is produced by recombinant DNA technology.

There are human insulins and human insulin analogues. The use of the insulins described below is for subcutaneous administration (regular and aspart insulin can also be administered intravenously in the hospital). Injected insulin is absorbed subcutaneously into the systemic circulation.

Most of the insulin formulations are dispensed in 100 units/mL or U100. If no indication is made, we are referring to U100.

Most of the information that is known, comparing the different types of insulin, has come from several "treat to target trials" [5–8], where the insulin dose of the different arms of a study was titrated to achieve a certain glycemic control and the incidence of hypoglycemia and weight gain was compared between the different arms.

Human insulins are rapid or regular-acting insulins (R) and intermediate-acting insulin (NPH). Rapid or regular-acting insulin is identical to human endogenous insulin. It is clear in solution. It takes 30 min to absorb after being subcutaneously injected. Regular-acting insulin has its peak of action 2–3 h after being administered and has a time of action of 4–6 h. This insulin is used as a prandial insulin or bolus, and it helps control postprandial glycemia. In cases of extreme insulin resistance, Regular Insulin U500 (500 units/mL) is available in the United States.

NPH or intermediate-acting insulin is a regular-acting insulin that is in solution with protamine, which makes it appear milky. It has a longer time of action, having its peak at 8–10 h after being injected, and its duration up to 10–14 h. However, at higher insulin doses, the duration of action is higher.

The advantages of human insulins (rapid and NPH) are the low costs and high availability in the market. The disad-

Table 37.2 Types of insulin and times of action

Types of insulin	Class	Start of action	Max peak	Duration
Fast-acting Lispro Aspart Glulisine	Analogues	5–15 min	30–90 min	3–4 h
Rapid-acting (regular)	Human	30–45 min	2–3 h	4–6 h
Intermediate (NPH)	Human	2–4 h	8–10 h	10–14 h
Long-acting Glargine U100 Detemir *Ultra-long- acting* Degludec Glargine U300	Analogue	1.5–2 h	No peak	18–24 h 24–40 h

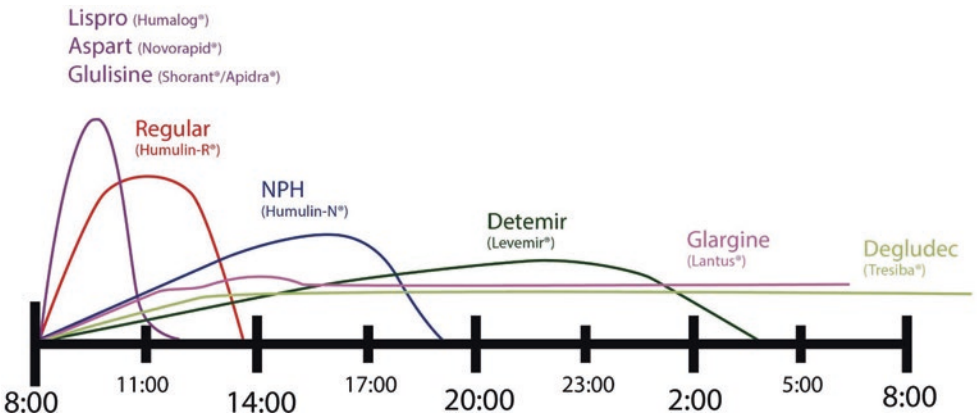

Fig. 37.2 Times of insulin action

vantages include that, due to its peak and duration of action, the risk of hypoglycemia is higher, especially if the patient does not have a strict feeding regimen, to match insulin peak and duration of action. In addition, NPH insulin has greater variability in its absorption and bioavailability, so it is less predictable, and in general, there is a higher incidence of hypoglycemia with its use.

In last decades, several insulin analogues have appeared in order to mimic more physiologically insulin action.

There are three fast-acting insulin analogues: lispro, aspart, and glulisine. Due to molecular modifications, after a subcutaneous injection, it takes 0–15 min to start their action, peak at 30–90 min, and last between 3–4 h. These analogues are used prandially or in bolus.

There are newer, faster-acting insulins, called ultrarapid acting; these insulins allow dosing to occur at the start of or even during a meal to better control postprandial glucose peaks. The first ultrarapid insulin, called fast-acting insulin aspart (Fiasp), was approved by the FDA in 2017 and contains insulin aspart formulated with 2 additional excipients, L-arginine that acts as a stabilizing agent and niacinamide that accelerates absorption in the site of injection [9, 10]. Another ultrarapid insulin, called ultrarapid lispro (Lyumjev), was approved by the FDA in 2021. It is a novel insulin lispro formulation developed to more closely match insulin secretion and improve postprandial glucose control. The approval trial (PRONTO-PUMP-2), demonstrated that it was superior in both 1-h and 2-h postprandial glucose reduction when delivered 0–2 min before meals [11].

There are two long-acting insulin analogues: glargine (U100; 100 international units per ml) and detemir. Insulin glargine is in solution at pH 4.0, but when injected at neutral pH, it forms crystals, and therefore, its absorption is slower. Insulin detemir has a 14-carbon fatty acid bound to the amino acid 29 of the beta chain, therefore having a higher affinity to albumin. This increases its half-life. These two insulins take 1.5–2 h to start its action and generally do not peak (although clinically they appear to have a small peak at 6–8 h from injection), and their duration of action is between 18 and 24 h. They are used as basal insulin one or two times per day. Both have shown to cause less hypoglycemia than NPH insulin. If insulin detemir is compared with glargine, the former has shown a discrete lower weight gain. The ORIGIN study [12] showed that insulin glargine given to patients with impaired fasting glucose and impaired glucose tolerance or T2D had similar cardiovascular outcomes to those patients that received the standard care.

There are two ultra-long-acting insulin analogues: degludec and glargine U-300.

In 2013, insulin degludec appeared in the market. Degludec insulin has a glutamic acid spacer bound to amino acid 29 of the beta chain and then a 16-carbon fatty acid. These changes allow it to be in di-hexamers in solution and, when injected, forms multi-hexamers. The monomers are then released one by one. Degludec has no peak and has a half-life of 24 h. It has low variability, can be applied once a day, and has flexibility in the injection schedule. In addition, a lower incidence of nocturnal hypoglycemia has been documented with this insulin, compared with glargine U100. Insulin degludec is available at U100 (100 units per mL) or U200 concentration (200 units/mL). In the United States, both formulations exist. In Mexico, only the U100. Both act similarly. Insulin Degludec was approved by the FDA in 2015. The DEVOTE study [13] (Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events), published in the NEJM in August 24th, 2017, showed that Degludec was non-inferior to glargine U100 with respect to incidence of cardiovascular events and again demonstrated a much lower risk of severe hypoglycemia and nocturnal hypoglycemia.

Another prolonged-acting insulin analogue appeared in the market, and this is insulin glargine U300 [14, 15] (300 international units per mL). By being more concentrated, it forms a compact subcutaneous depot with a smaller surface area, to produce a more gradual and prolonged release. Compared to Glargine U100, it has shown lower event rates

of nocturnal hypoglycemia. Glargine U300 can be injected with a 3 h flexible regimen.

There are pharmacokinetics studies [16] that compare degludec to Glargine U300. The clinical studies have not shown a significant difference in the rate of hypoglycemia between the two types of insulin [17].

In general, the advantages of insulin analogues are as follows: more bioavailable, less variable, more predictable, more physiological, better glycemic control, and less hypoglycemia.

The disadvantages are higher number of injections and higher cost.

There are once-weekly basal insulins under development (preclinical to phase 2 studies) that promise to have greater convenience, easy to overcome clinical inertia, better treatment adherence, ensure glycemic control, and low risk of hypoglycemia.

Premixed insulins have a fixed proportion of intermediate insulin with rapid- or fast-acting insulin. Insulin 70/30 consists of 70% NPH and 30% rapid-acting insulin. There is premixed insulin with 70% intermediate-acting insulin (aspart-protamine, NPA) and 30% insulin aspart. There are two premixed insulin concentrations: one with 75% intermediate insulin (lispro-protamine, NPL) and 25% insulin lispro and the other with 50% insulin NPL and 50% insulin lispro, which is more physiological and could be used three times per day, before each meal.

The advantages of premixed insulin are mistake minimization, ease of use, increased treatment adherence, and fewer injections.

The disadvantages are fixed dose and less flexibility and may increase the risk of hypoglycemia if a fixed meal schedule is not followed.

There is a co-formulation (IDegAsp, Ryzodeg) 70% insulin degludec and 30% insulin aspart solution in a pen. The advantage of this co-formulation is that it has a significant reduction in the incidence of nocturnal hypoglycemia compared to the premixed insulin with NPA and insulin aspart 70/30. This co-formulation can be applied once or twice per day and is a useful and simple alternative for patients with T2D.

In addition, there are two new combinations between long-acting insulin analogues and GLP-1ra [18]. These are degludec insulin with liraglutide (iDegLira) and insulin glargine with lixisenatide (iGlarLixi).

The combination of degludec insulin with liraglutide (100 units/mL and 3.6 mg/mL, respectively) is indicated once daily, as an adjunct to diet and exercise, to improve glycemic control in adults with T2D inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily).

The combination insulin glargine and lixisenatide (100 units/mL and 33 μg/mL and 100 units/mL and 50 μg/mL respectively) is indicated for once-daily dosing covering 15–60 units of insulin glargine and 5–20 μg of lixisenatide.

The advantages of these combinations are the lower risk of hypoglycemia, decreased insulin doses, less weight gain, and the possibility of lower cardiovascular risk, when compared to basal-bolus insulin regimens.

Describing further the use of these two combinations is beyond the scope of this chapter, but one should be familiarized with these new options. The reader is invited to review the prescribing information for each country, when available. Both were approved in the United States by the FDA in 2017.

Inhaled Insulin [19–22]

There have been several lines of research work to administer insulin through other routes, being the inhaled form, the one that has reached the market. Exubera, an inhaled form of rapid acting insulin developed by Pfizer, became the first inhaled insulin product to be marketed in 2006, but due to poor sales, it was withdrawn from the market in 2007. Afrezza, developed by Mannkind, uses a different technology (technosphere) and was approved by the FDA in 2014 for use in both T1D and T2D. It contains recombinant human insulin dissolved with powder (fumaryl diketopiperazine). Once inhaled, technosphere insulin is rapidly absorbed upon contact with lung surface. Both components, insulin and powder (fumaryl diketopiperazine) are almost completely cleared from the lungs of healthy individuals within 12 h of inhalation. As it has rapid absorption, it can be used as prandial insulin. Currently, it is dispensed in a small inhaler, and insulin cartridges come in 4, 8, and 12 units. It may cause hypoglycemia, cough, and throat pain/irritation, as well as acute bronchospasm in patients with asthma and COPD. As of this writing, it is only available in the United States.

Insulin Management Regimens (Figs. 37.1 and 37.3 and Appendix)

As already mentioned, insulin can be used from T2D diagnosis, in its late phases, or at times of diabetes decompensation.

All insulin regimens have a "starting" and "adjustment" phase.

In the "starting phase," the prescribed dose is calculated, as it will be seen later in each regimen.

In the "adjustment phase," it is observed through SMBG and how the person responded to therapy, and adjustments are made to avoid hypoglycemia and hyperglycemia.

In the adjustment phase:

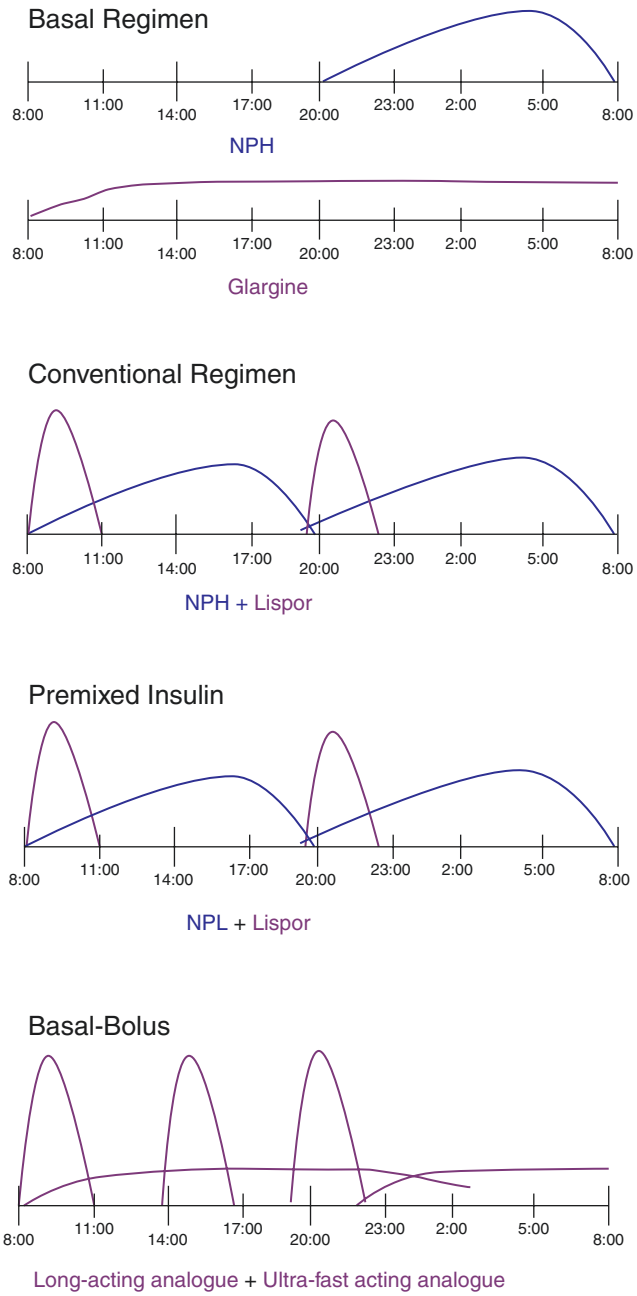

Fig. 37.3 Insulin regimens

- The insulin dose that affects fasting or preprandial glucose is adjusted according to whether there is hyperglycemia (>120–130 mg/dL- 7 mmol/L) or hypoglycemia (<70–80 mg/dL- 4 mmol/L).
- The insulin dose that affects postprandial glucose is adjusted according to whether there is hyperglycemia (>180 mg/dL- 10 mmol/L) or hypoglycemia (<100 mg/dL- 5.6 mmol/L).
- Only one dose is adjusted at a time.
- Adjustment is imperative when there is hypoglycemia.
- If there is hyperglycemia, it is preferred to observe the pattern over 3 days. Then, the adjustment consists of increasing or decreasing ≈2 U the dose of insulin, which was responsible for that glucose value.

Basal Insulin Regimen [1]

When basal insulin is prescribed, an intermediate-acting, long-acting, or ultra-long-acting nocturnal insulin injection is chosen; however, with some of the long- and ultra-long-acting insulin analogues (detemir, glargine U100 or U300, degludec), it could also be administered in the morning.

For nocturnal dosing, intermediate-acting insulin (NPH), long-acting insulin analogues (glargine U100, detemir), or ultra-long-acting (degludec, glargine U300) may be chosen. The advantages of insulin analogues are that they cause less nocturnal hypoglycemia. The starting dose is usually 10 units or 0.2 units/kg/day.

When intermediate-acting insulin or detemir insulin is used, dose adjustment should be done every 3 days. The adjustment consists in increasing or decreasing the dose 2–3 units (or 10–20% of basal dose), depending on whether there is hyperglycemia or hypoglycemia according to the monitoring of fasting glucose, until the glycemic control goal is achieved. With these insulins, when the basal total dose is greater than 0.3 units/kg/day (22–26 units), it is advisable to divide the dose into two injections (morning and evening) to avoid nocturnal hypoglycemia.

When glargine or degludec insulin is used, dose adjustment is preferably done every 5–7 days (although it can be adjusted earlier if the person is not controlled). With these insulins, it is generally not necessary to fractionate the dose into two injections, unless the insulin glargine U100 or detemir is not lasting 24 h.

It should be mentioned that if a patient who is already using NPH insulin switches it to glargine U100 (perhaps to avoid an increased risk of nocturnal hypoglycemia), 80% of the NPH dose should be used. That is, if 20 units of NPH insulin were used, when switching to glargine U100, only 16 units of NPH should be used. If a patient is changed from insulin glargine U100 to insulin degludec, prescribing information indicates that the same dose should be used, but in the author's experience, patients require a 20% lower dose of degludec. In addition, when changing from insulin glargine U100 to U300, a higher dose may be required (10–20% more dose).

Intensive Regimens (Figs. 37.1 and 37.3)

Over time, some patients that use basal insulin may require prandial insulin coverage, and this can be done with the different insulin regimens:

- Conventional regimen: NPH twice per day plus rapid- or fast-acting insulin analogues two or three times per day.
- Premixed insulin: Twice or three times daily.
- Basal-plus: Basal plus prandial insulin for a single meal coverage.
- Basal-plus a GLP-1ra.
- Basal-bolus: Basal plus prandial insulin for more than one or for all meals.

Conventional Insulin Regimen

In this regimen, the patient uses NPH insulin and rapid-acting insulin or fast-acting insulin analogues twice a day. The advantages of this regimen are that usually only two injections per day are needed and of lower cost and that the morning rapid-acting insulin covers lunch/snack and morning NPH covers the glucose elevation caused by food intake at lunch/late lunch.

The disadvantages are that it is not flexible, and the patient must have a strict feeding schedule to avoid hypoglycemia, and there is an increased risk of nocturnal hypoglycemia.

The initial dose usually starts in 0.5 units/kg/day.

The total insulin dose is divided in 2/3 in the morning and 1/3 in the evening.

The morning dose (pre-breakfast) is further fractionated in 2/3 for NPH insulin and 1/3 for rapid or fast-acting insulin.

The evening dose (pre-dinner) is fractionated in 2. Half for the NPH insulin and half for the rapid or fast-acting insulin (pre-dinner insulin) can also be divided into 2/3 NPH and 1/3 rapid- or fast-acting insulin.

Insulin should be injected 30 min before meals if it is a rapid-acting insulin and 0–15 min prior meals if it is fast-acting insulin analogue.

In case the conventional regimen is used with NPH and rapid-acting insulin, it is of vital importance for the patient to include snacks:

- In some countries, lunch is eaten at noon, and a snack will be required around 3:00 or 4:00 p.m.
- In others, the main meal of the day is at around 3:00 p.m., and a snack will be required around 11:00 a.m. to 12:00 noon.
- In addition, a snack must be included before going to sleep.

However, if the conventional regimen is used with NPH and fast-acting insulin analogues, snacks may or may not be needed. However, for countries where lunch is eaten at noon, usually a small snack (15 g of carbohydrates) will be needed at 3:00 or 4:00 p.m. In general, a snack will be required at bedtime.

Example

Sixty-year-old male that weighs 72 kg. If his dose is calculated at 0.5 units/kg/day, he would need a total of 36 units. Two thirds are going to be injected before breakfast (24 units) and one third before dinner (12 units). Of the 24 units that should be administered before breakfast, 16 units are NPH and 8 units of rapid- or fast-acting insulin. Of the 12 units that have to be injected before dinner, 6 units are NPH, and 6 units are rapid- or fast-acting insulin, although this last dose can be adjusted downward if the patient eats a small meal.

Subsequently, treatment adjustments are made.

If there is morning hyperglycemia, it should be ruled out that it is not secondary to a 2:00–3:00 in the morning hypoglycemia followed by hyperglycemia (Somogyi phenomenon or excessive carbohydrate intake to correct said hypoglycemia) or because of the Dawn phenomenon (surge in cortisol production from 3:00 to 8:00 in the morning, with increased hepatic glucose production). This is ruled out by checking the blood glucose before dinner, after dinner, at 3:00 a.m., and upon awakening.

If hypoglycemia occurs, the dose of NPH can be reduced by 2–3 units, and see if morning hypoglycemia is avoided. If not, NPH can be administered at night (10:00–11:00 p.m.), so that its peak of action is at 6:00–7:00 a.m., when the patient awakes. If nocturnal hypoglycemia cannot be avoided, NPH insulin could be switched to a long- or ultra-long-acting analogue such as glargine U100, detemir, degludec, or glargine U300.

If there is no Somogyi phenomenon and fasting glucose is elevated, then the nocturnal NPH insulin dose should be increased by 2 units every 3 days until the glycemic control goal is reached (70–80 mg/dL–120–130 mg/dL–4–7 mmol/L).

Once fasting glucose is controlled, SMBG is required before and 2 h after each meal for the next 2–3 days order to see if there are any glucose patterns. In order to adjust the morning dose of NPH insulin, and then the doses of rapid or fast acting insulin that are applied before meals.

- If there is hyperglycemia (>130 mg/dL—7 mmol/L) before lunch or dinner, morning NPH insulin can be increased by 2 units. If there is hypoglycemia, then the dose is reduced by 2 units.
- The rapid- or fast-acting insulin dose applied before meals is adjusted in case of 2 h postprandial hyperglycemia (>180 mg/dL–10 mmol/L) or postprandial hypoglycemia (<100 mg/dL–5.6 mmol/L). The insulin dose is increased or decreased by 2 units, respectively.

Premixed Insulin

Premixed insulins contain a similar proportion to that described above of intermediate insulin (50–75%) and rapid- or fast-acting insulin (25–50%); a "conventional" treatment

can be initiated. In this case, the dose is calculated in the same way (0.5 units/kg/day), which is divided in 2/3 before breakfast and a 1/3 before dinner.

The adjustment is made in a similar manner to that described in the conventional regimen.

The dose of insulin injected before dinner is adjusted by assessing fasting blood glucose.

The dose of insulin that is injected before breakfast is adjusted by assessing premeal glycemia.

For someone who has breakfast at 7:00 in the morning, main meal at 16:00 h. and dinner at 23:00 h, the premixed total insulin could be divided in three, and each third is given before breakfast, main meal, and dinner. The appropriate adjustments, are made according to SMBG results.

Basal Plus

The stepwise study [23, 24] proposes that patients who already use long-acting insulin should initiate fast-acting insulin before a single meal (the most abundant or the one with the highest postprandial glucose levels) and gradually increase injections in different meals to achieve a better glucose control. Although rapid-acting insulin may be used, fast-acting insulin analogues are preferred.

There are three ways to calculate this dose:

(a) Starting an initial dose of 2–4 insulin units of fast-acting insulin analogues could be administered before that meal and adjust depending on 2 h postprandial glucose levels. Increasing or decreasing by 2 units until an adequate postprandial glucose level is achieved.
(b) Calculating the prandial insulin at 0.1 units/kg.
(c) Calculating the prandial insulin as 10% of the basal dose. If the HbA1c is lower than 8%, one may consider reducing the basal dose, by the same amount of units of the prandial insulin that was started.
(d) Calculating one insulin unit for each carbohydrate portion (15 g), taking into account that the patient shouldn't eat more than 4 portions of carbohydrates (60 g) per meal. So, 4 units of insulin would be administered for 60 g of carbohydrates.

Adjustments should be made, by increasing or decreasing 2 units until the postprandial glycemic target (140–180 mg/dL–7.8–10 mmol/L) is reached.

A new way to start the basal-plus regimen is by using the co-formulation of degludec insulin (70%) and aspart insulin (30%) called Ryzodeg. This can be started with a dose of 0.2–0.3 units/kg/day. This must be injected before the main meal or the one that most increases the postprandial glucose levels.

Basal-Plus GLP-1ra

One could also have a regimen of basal insulin plus a GLP-1ra, either in combination or given separately. In general, the insulin dose will need to be adjusted downward, when adding a GLP1ra.

Basal Bolus

The basal-bolus regimen has more schedule flexibility, lower weight gain, and lower risk of hypoglycemia than the conventional regimen. However, for the flexible basal-bolus regimen, carbohydrate counting is required, and the patient must have the capacity and willingness to do mathematical calculations. With this regimen, it is not necessary for the patient to make snacks. If the patient does not want to count carbohydrates, he can be given a fixed diet and a fixed amount of fast-acting insulin before each meal (fixed basal-bolus). In the basal-bolus regimen, the patient starts with 0.5 units/kg/day.

Fixed Basal Bolus

In the fixed basal-bolus regimen, the patient starts with 0.5 units/kg/day. The total insulin dose is fractionated in the following way:

- 50% of the total insulin dose is the basal one. It can be used with insulin glargine U100 or U300, detemir, or degludec. These are usually administered once a day. In the case of glargine U100 or detemir, they may need to be divided in two doses (12 h apart), if it is observed that a single dose is having a peak or if the effect lasts less than 24 h.
- 50% of the total dose is for the boluses, which cover meals and correct elevated blood glucose levels. For boluses, fast-acting analogues such as lispro, aspart, or glulisine are usually used, although rapid-acting insulin can also be used. Usually, the assigned dose for the boluses is divided between the 3 meals of the day.

For example, if a patient weighs 72 kg and we calculate his dose at 0.5 units/kg/day, he would need a total of 36 units per day. Half of them, which is 18 units, are used for the basal and the other half for the bolus. If the 18 units are divided between the 3 meals of the day, the patient would have to inject 6 units before each meal.

If the patient is going to eat a small meal, he can inject only 4 units, but if it is a large meal, he is going to need 8 insulin units.

In addition, the correction factor can be calculated in case the preprandial glucose is above 150 mg/dL, and an extra dose of fast-acting insulin can be administered to correct glucose levels, for example, 1 unit per 50 mg/dL above 150 mg/dL. That is, if the patient had 250 mg/dL of glucose, in addition to the 6 units of the meal bolus, 2 more should be added to correct glucose levels. A total of 8 insulin units should be injected before said meal.

Flexible Basal Bolus (Figs. 37.4, 37.5, and 37.6, Appendix)

It also starts with a dose of 0.5 units/kg/day, and also, 50% of the insulin is basal and 50% prandial (Fig. 37.4).

To calculate the boluses, the insulin-to-carbohydrate ratio and the correction factor are used.

The insulin-to-carbohydrate ratio shows how many grams of carbohydrates are covered by the injection of one unit of insulin. Said ratio is usually initially calculated by the 450 rule [25], meaning that it is obtained by dividing 450 by total daily insulin dose (TDD), when fast-acting insulin is used.

As an example, if the person uses a total of 30 units of insulin per day, then we divide: 450/30 = 15. That is, one unit

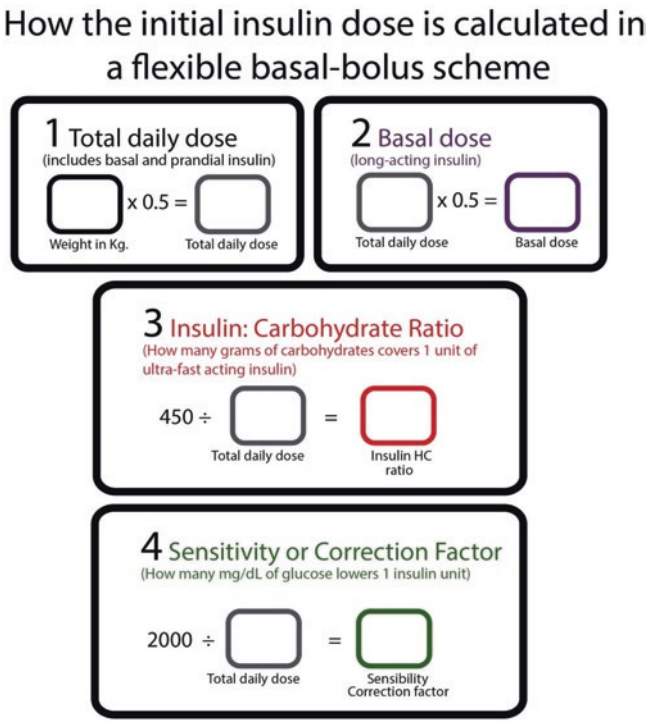

Fig. 37.4 How the initial insulin dose is calculated in a flexible basal-bolus scheme

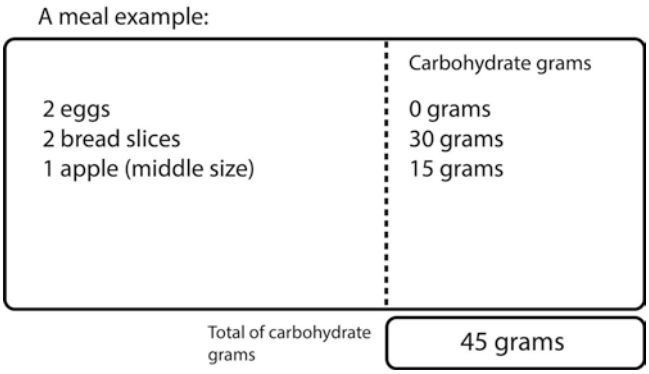

Fig. 37.5 A meal example

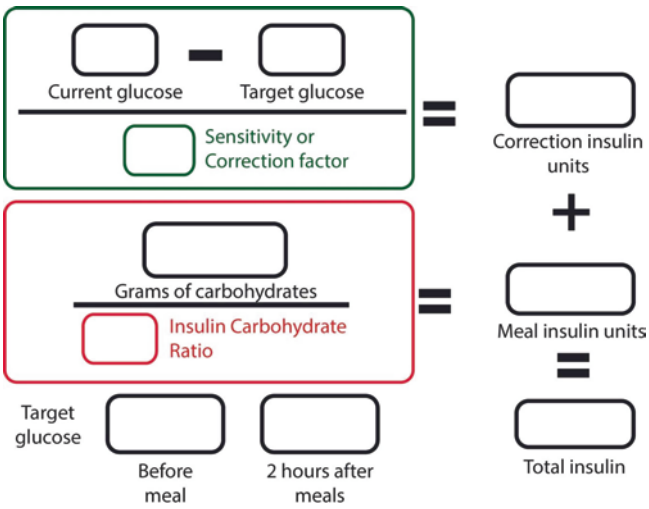

Fig. 37.6 Calculations that the patient makes to decide the insulin bolus (for both correction and meal coverage)

of fast-acting insulin would be injected for every 15 g of ingested carbohydrates. For example, if 45 g of carbohydrates are eaten, the patient would inject 3 units of fast-acting insulin (45/15 = 3) (Fig. 37.5).

It is important to tell the patient to preferably limit his carbohydrate intake to a maximum of 60 g per meal so that insulin works better.

It must be pointed out that the actual insulin-to-carbohydrate ratio could be calculated by dividing 300–500 by the TDD, although starting at 450 is safe.

The sensitivity or correction factor shows how many mg/dL of glucose are lowered by the injection of one unit of insulin. This is commonly calculated by dividing 2000/TDD (if using mmol/L, it can be done by dividing 100/TDD).

Continuing with the example: 2000/30 = 66.66 that can be rounded to 70 mg/dL.

The initial goal is 150 mg/dL of glucose. If the patient has 220 mg/dL of glucose and wants to reach 150 mg/dL, the difference is 70 mg/dL. Divided by the correction factor of 70 mg/dL, it resolves that the patient has to inject himself 1 unit of extra fast-acting insulin to his prandial insulin dose.

It must be pointed out that the actual sensitivity factor could be calculated by dividing 1500–2000 by the TDD, although starting at 2000 is safe. For deeper reading on the initial insulin-carbohydrate ratio and correction factor, please refer to the papers by John Walsh et al. [26, 27].

Figure 37.6 shows how a patient must do all the calculations to decide the insulin dose he should inject before each meal.

During the adjustment phase, the patient should perform SMBG before all meals and preferably 2 h postprandial and 2 h after a correction has been administered.

If the patient presents with hyper- or hypoglycemia 2 h after a meal, it should be checked if the carbohydrate count-

ing was adequate. If an error was not detected, the insulin-to-carbohydrate ratio should be changed. For example, in the case of hyperglycemia, the ratio could be changed from 1:15 g to 1:12 g of carbohydrates. If the patient was injecting 4 units for 60 g of carbohydrates, now he will be injecting 5 units for the same quantity of carbohydrates.

In the case of hypoglycemia, the insulin-to-carbohydrate ratio could be changed from 1:15 g to 1:20 g of carbohydrates. If the patient was injecting 4 units every 60 g, now he is going to inject himself with 3 units.

Also, in the case of hyperglycemia or hypoglycemia after a correction bolus, all factors that contributed to this situation should be reviewed (exercise, stress, illness, fasting, menstruation, etc.). If no reason is found, the correction factor should be changed.

In the case of hyperglycemia after a correction, the sensitivity factor can be changed from 1:70 mg/dL to, for example, 1:50 mg/dL.

In case of hypoglycemia after a correction, the sensitivity factor may be changed from 1:70 mg/dL to 1:100 mg/dL, for example.

It is important to stress out that the insulin-to-carbohydrate ratios and the sensitivity factors may be different throughout the day.

Basal Bolus with Sliding Scale

This regimen is a variation of the fixed and flexible basal-bolus regimens, where the total daily dose (TDD), the percentage of the basal dose, and the dose for the boluses are calculated the same way as in the fixed basal-bolus, but a table or sliding scale is given to the patient so that depending on the patient's pre-prandial glucose, insulin units are injected.

The quantity of insulin is also initiated at 0.5 units/kg/day. This dose is fractionated in 50% basal and 50% for boluses. The bolus dose is also divided by 3, and that is the number of insulin units that should be injected before every meal. The correction factor is also calculated with the formulas previously described in the flexible basal-bolus. An example of the table for basal bolus is shown below.

Glucose (mg/dL)	Before breakfast	Before lunch	Before dinner	2-h postprandial
<70				
71–100				
101–150				
151–200				
201–250				
251–300				
301–350				
351–400				
>400				

For example, if a patient weighs 72 kg and the starting dose is 0.5 units/kg/day, he would need 36 units per day. He would use 18 units for the basal dose and 18 units for the bolus dose. 20 units are further divided by three meals. So, he would have to inject himself 6 units of fast-acting insulin before every meal. The correction factor is calculated by dividing 2000/36, which is equal to 55 mg/dL, and this is rounded to 50 mg/dL. It is important to tell the patient to have a fixed amount of carbohydrates per meal (e.g., 45–60 g).

The table is filled in the following way:

Glucose (mg/dL)	Before breakfast	Before lunch	Before dinner	2-h postprandial
<70	3	3	3	0
71–100	4	4	4	0
101–150	6	6	6	0
151–200	7	7	7	0
201–250	8	8	8	2
251–300	9	9	9	3
301–350	10	10	10	4
351–400	11	11	11	5
>400	12	12	12	6

Insulin Pumps

Insulin can be applied with syringes, pens, and insulin pumps. Insulin pumps are electromechanical portable devices that function through batteries and administer rapid- or fast-acting insulin through a catheter connected to a subcutaneous cannula in the patient's abdomen. The cannula is changed every 3 days. The insulin from the insulin pump is located in a deposit or cartridge, and it is automatically administered through a basal dose. Plus, the patient programs a feeding bolus (prandial) or a correction bolus. For more information, please refer to Chap. 38

Insulin Adverse Effects

The adverse effects of insulin include hypoglycemia, edema, and weight gain. If the patient always injects the insulin in the same place, he could develop lipohypertrophy and lipoatrophy. In order to avoid these situations, the place in which the insulin is injected should be rotated. To avoid hypoglycemia, it is important to educate the patient regarding SMBG technique and tight glucose monitoring, as well as hypoglycemia treatment. For more information, please refer to Chap. 45.

Before initiating intensive therapy with insulin, it is important to rule out the presence of proliferative retinopathy through a dilated-pupil fundus examination. If present, the blood glucose target should be reached at a slower rate. It is known that pre-existent, diabetic proliferative retinopathy can increase initially with intensive insulin therapy, although it later improves [28].

Storage and Insulin Application Techniques

Insulin is stored in the refrigerator, not in the freezer, and should be taken out 30 min before use. If desired, the insulin in use may be maintained at room temperature, as it is stable for 28 days. Insulin Degludec is stable for 2 months outside the refrigerator at room temperature.

Insulin can be applied using syringes, pens, or insulin pumps. Syringes of 30, 50, and 100 units exist. Most of the 30 unit syringes have the measure of half units, which are very useful for people who are very sensitive to insulin or for children. Those of 50 units go from unit to unit and those from 100 units from two to two units. Syringe needles range from 6 to 13 mm in length.

There are rechargeable and disposable pens. In the rechargeable ones, the 3 mL cartridge is inserted and can be reused with new cartridges. The disposable ones come with an integrated 3 mL cartridge and are thrown away when finished. The needles for the pens are 4–8 mm long, and the lowest thickness is 32G. Insulin should be injected subcutaneously. To avoid intramuscular injection, it is best to use the shorter needles.

The insulin NPH and the premixed insulins should be mixed by turning the bottle between the hands (like rolling a pen between hands) to bring it to a uniform suspension. Do not shake to avoid bubbles. Once mixed, the lid of the vial is cleaned with a cotton swab moistened with alcohol. The plunger of the insulin syringe is pulled up to the number of insulin units that the patient requires. Air is injected into the insulin vial to break the vacuum effect and to facilitate the exit of the insulin. Immediately, afterward, the insulin bottle is turned around, without removing the syringe. Then the syringe is removed, taking care that no bubbles form. The top of the syringe plunger should be in the line of insulin units.

When insulins are mixed up in the same syringe, the rapid-acting insulin or the fast-acting insulin analogues are extracted first and secondly the NPH insulin. NPH mixed with rapid-acting insulin is stable in the syringe and can be left in the refrigerator for later use (e.g., if one prepares insulin for another person to use later). NPH mixed with insulin analogues (lispro, aspart, glulisine) is not stable; therefore, it should be injected immediately after it is loaded. Insulin glargine cannot be mixed with any fast-acting or ultra-rapid-acting insulin because of its pH. The syringe needle should not touch the fingers of the patient, cotton swab, or anything else, as it would contaminate and could cause skin infections.

Insulin application technique is as follows:

1. Select a site for injection.
2. Clean the skin with a cotton swab.

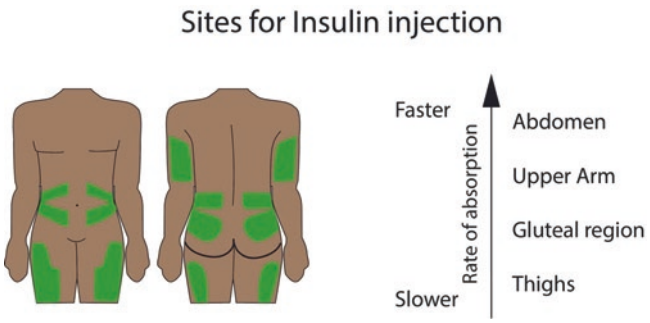

Fig. 37.7 Sites for insulin injection

3. Pinch approximately 2–3 cm of skin.
4. Hold the syringe in the same manner as a pencil is taken.
5. Insert the needle into the fold formed between the fingers in a 45° angle (thin patient) or 90° (obese patient).
   (a) The faster the needle is inserted, the less it hurts.
6. Release the crease.
7. Push the plunger gently until all the insulin has passed.
8. Wait 10 s before withdrawing the needle.
   (a) It is drawn in the same direction as it was introduced, gently pressing with a cotton swab at the injection site. Do not rub or massage the area.

Factors that affect insulin absorption should be taken into account such as:

- Site (Fig. 37.7)
- Depth of injection
  - Intramuscular. If injected by mistake, absorption will be faster.
- Dose
  - The higher the dose, the longer the effect of insulin.
  - This does not apply to insulin lispro, aspart or glulisine.
- Exercise
  - If insulin is injected in a site that it is about to be exercised, absorption will be faster.
- Temperature
  - At higher temperature, insulin absorption is faster and vice versa.

Conclusions

The different types of insulin have been reviewed as well as the different regimens of insulin application. When using basal insulin, the initial dose is 0.2 units/kg/day. An insulin titration algorithm should be given to the patient so that he can reach his glycemic goal faster. If the basal insulin dose reaches 0.3–0.5 units/kg/day, one must divide the basal insulin in two doses per day. Also, one should start considering adding prandial insulin, especially if the glycemic goal has

not been reached. One must be careful not to use the basal insulin to cover the prandial requirements.

When a more complex insulin regimen needs to be implemented, one has to decide whether to use the conventional regimen, the premixed insulins, a basal plus prandial, a basal plus GLP-1ra, or a basal-bolus regimen.

In general, for the conventional or basal-bolus regimen, the starting dose is 0.5 units/kg/day. This will then be divided between basal and prandial insulin. Basal-bolus insulin can be given in a fixed schedule, in a flexible schedule (insulin-to-carbohydrate ratio and sensitivity factor), or with a sliding scale.

In patients with T2D, if metformin use can be maintained, lower doses of insulin are required. Sulphonylureas should be discontinued to decrease the risk of hypoglycemia. In addition, if GLP1ra are used, lower insulin doses will be required, and the risk of hypoglycemia will be lower.

Most patients will achieve good glycemic control with 0.5–1.0 units/kg/day. Adolescents may require 1.0–1.5 units/kg/day. When more than 1.5 units/kg/day are required, then there is important insulin resistance.

The physician should analyze and suggest the regimen that will best help the patient achieve the individual goal of glycemic control.

This will decrease the incidence of complications of diabetes, which are already a severe problem in public health because of the high economic, social, and emotional cost that is involved.

Concluding Remarks

1. There are several types of insulin, depending on their insulin action time:
   (a) Fast acting (lispro, aspart, glulisine)
   (b) Rapid acting (regular)
   (c) Intermediate acting (NPH)
   (d) Long acting (detemir, glargine U100)
   (e) Ultra-long acting (degludec, glargine U300)
2. The main insulin adverse effects are hypoglycemia and weight gain.
3. Glargine U100 and detemir insulin cause less hypoglycemia than NPH insulin.
4. Detemir insulin causes less weight gain than glargine U100 and NPH.
5. Degludec and Glargine U300 cause less hypoglycemia than Glargine U100.
6. There are several insulin regimens, and each has an initiation phase and an adjustment phase. One should choose the regimen that best fits the patient.
7. Insulin regimens include the following:
   (a) Basal
   (b) Intensive regimens:
   - Conventional
   - Premixed insulin
   - Basal-plus prandial insulin
   - Basal-plus GLP-1ra
   - Basal bolus
     – Fixed
     – Flexible
     – Sliding scale
     – Insulin pump therapy

Multiple Choice Questions

1. Which insulin helps control glucose production by the liver?
   (a) Basal
   (b) Prandial
2. Which type of diabetes is characterized by an absolute insulin deficiency?
   (a) Type 1 diabetes
   (b) Type 2 diabetes.
   (c) Neonatal diabetes
   (d) MODY
3. To avoid diabetic ketoacidosis, patients with type 1 diabetes mellitus should continue their treatment with:
   (a) Insulin
   (b) Sulphonylureas
   (c) Metformin
   (d) Thiazolidinediones
4. Which is the main adverse effect of insulin therapy?
   (a) Blindness
   (b) Hyperglycemia
   (c) Hypoglycemia
   (d) Diabetic ketoacidosis
5. Which one is NOT an indication for initiation of insulin therapy?
   (a) Patients with type 1 diabetes
   (b) Newly diagnosed patients with type 2 diabetes who are very symptomatic
   (c) Patients with type 2 diabetes who have a glycosylated hemoglobin A1c $\leq$ 7%
   (d) Patients with type 2 diabetes who have progression of chronic microvascular complications
6. Examples of fast-acting insulin analogues are:
   (a) Rapid insulin
   (b) Insulin lispro, aspart, and glulisine
   (c) Insulin detemir and glargine
   (d) NPH insulin
7. Are some advantages of insulin analogues EXCEPT:
   (a) Less predictable
   (b) More physiological
   (c) Provide better glycemic control
   (d) Less hypoglycemia

8. Which is usually the starting dose for basal insulin?
   (a) 0.8 units/kg/day
   (b) 0.6 units/kg/day
   (c) 0.4 units/kg/day
   (d) 0.2 units/kg/day
9. Which is NOT an intensive insulin regimen?
   (a) Basal + GLP-1
   (b) Basal plus
   (c) Basal
   (d) Premixed insulin
10. Which is NOT true about insulin storage?
   (a) It should be stored in the freezer.
   (b) Should be taken out 30 min before its use.
   (c) May be maintained at room temperature for 28 days.
   (d) Should be stored in the central compartments of the refrigerator.

Appendix: Initial Doses for Each Regimen

Basal insulin:

0.2 units/kg/day or 10 Units (Usually in the Evening)

Conventional Insulin Regimen:

0.5 units/kg/day

Divide

Option A

2/3 in a.m. (2/3 NPH, 1/3 rapid or fast acting).

1/3 in p.m. (1/2 NPH, 1/2 rapid or fast acting).

Option B

1/3 before every meal (1/2 NPH, 1/2 rapid or fast acting).

Basal Bolus Insulin Regimen:

Fixed basal-bolus

0.5 units/kg/day

−50% for basal doses.

−50% for prandial doses, divided in three equal doses. One for each meal.

Flexible basal-bolus.

0.5 units/kg/day (Total Daily Dose: TDD)

−50% for basal doses.

−50% for prandial doses.

Insulin to Carbohydrate Ratio (I:CHO ratio).

I:CHO ratio = 450/TDD.

Prandial bolus: Total of carbohydrate grams/I:CHO ratio.

Correction Factor:

mg/dL: Correction Factor = 2000/TDD.

mmol/L: Correction Factor = 100/TDD.

Pre meal target glucose: Initially 150 mg/dL (~8 mmol/L), later on 120 mg/dL (~7 mmol/L). If the patient is stable and is able to identify hypoglycemia, target glucose could be lowered to 100 mg/dL (5.55 mmol/L).

Post meal target glucose: 180 mg/dL (10 mmol/L).

Correction bolus = (Current glucose – Target glucose)/ Correction factor.

Total Bolus: Prandial Bolus + Correction Bolus.

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[1]To access useful information and resources about the topic in Spanish consult. https://clinicaendi.mx/recursos-impresos/

Insulin Pump Therapy

38

Raquel N. Faradji, Elena Sainz de la Maza, and Juan Ramón Madrigal Sanromán

Learning Objectives

- To identify the components of continuous subcutaneous insulin infusion (CSII) therapy.
- To assess the advantages, disadvantages, and considerations of CSII.
- To apply how to calculate the initial dose settings and the fine-tuning adjustments step by step.
- To describe the key issues of CSII on special situations.

How It Works: The Basics

Continuous subcutaneous insulin infusion (CSII) therapy uses a portable device that delivers rapid human insulin or fast-acting insulin analogues subcutaneously, via a cannula. The insulin delivery system tries to mimic the endogenous pancreatic insulin secretion and does this via two different features:

1. Basal rate: preprogrammed micro-boluses every few minutes throughout the day.
2. Bolus: patient can give extra insulin doses to cover food intake or to correct an elevated blood glucose (BG) level.
   (a) *Food bolus:* the patient indicates to the pump the BG level at that moment and the carbohydrate intake (in grams or portions), and the pump calculates the insulin amount, based on the insulin-to-carb ratio (ICR).
   (b) *Correction bolus:* the patient introduces the BG level at that moment, and the pump calculates the insulin amount based on the insulin sensitivity factor (ISF) and the BG target.

Insulin Pump Candidates

- Patients with type 1 diabetes (T1D) or type 2 diabetes (T2D) on intensive insulin therapy.
- Women with diabetes who are pregnant or are planning a pregnancy.
- Patients' age or diabetes duration should not be a determining factor in the transition to this therapy [1, 2].

Patient Requirements

- Responsible and psychologically stable.
- Motivated to achieve optimal BG control.
- Able and willing to carry out the tasks of this therapy safely and effectively and to maintain frequent contact with a healthcare team provider with full training and comprehension of CSII therapy.
- Able and willing to check their BG levels at least four times a day.
- Pediatric patients must have a motivated and committed family with a good understanding of diabetes self-management principles [1, 3].

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J. Rodriguez-Saldana (ed.), *The Diabetes Textbook*, https://doi.org/10.1007/978-3-031-25519-9_38

Advantages of CSII Therapy

- The micro-boluses, as low as 0.025 international units (IU) in some devices, allow to adjust with more precision to the requirements of the patient, which reduces hypoglycemia risk.
- The basal infusion can be temporarily augmented, reduced (temporal basal rates), or suspended, which can be useful to maintain BG control during sick days or exercise.
- The significant reduction in the number of insulin injections from 4 or more each day to one infusion set change every 3 or 4 days.
- Different bolus delivery options, described later in this text.

Disadvantages of CSII Therapy

- Psychosocial issues: as the user has to wear a device attached to his body day and night.
- Most of the available models in the market may be disconnected for periods no longer than 1 h, for example: taking a bath, swimming, or having high contact sports.
- Running out of insulin infusion for more than 2 h increases the risk of diabetic ketoacidosis (DKA). This can occur either because of remaining disconnected, air bubbles in the catheter, cannula obstruction, for example. This is the reason why patients have to check their BG often (at least four times a day). And if the BG is higher than 240 mg/dL (13.3 mmol/L) in two occasions, they must take action and correct with insulin injection and insulin, insulin reservoir, and infusion set change. They should be trained to always carry with themselves an extra infusion set change and an insulin delivery device like insulin pen or syringes and an insulin vial.

Types of Insulin Pump

There are different kinds of insulin pumps in the market:

- With tubing: insulin pump device connected via a catheter (from 18 to 43 inches length) to a subcutaneous cannula.
- Without tubing (patch pumps): insulin infusion device that includes the cannula, reservoir, and infusion mechanism inside. Some models include the controller components on the pump, and others communicate wirelessly with a separate controller device. The insulin pump configuration is set in the controller device, both for the basal rate and the bolus calculation. They are waterproof, and some are approved for depths of 25 ft for 60 min.
- With or without continuous glucose monitoring (CGM): Some models are just compatible with a CGM and give hypo- and hyperglycemia alarms, but the device does not take any action with the information the CGM provides. Other models are integrated with the CGM system and can take some actions to prevent hypoglycemia, such as stopping the infusion at a low glucose reading (low glucose suspend feature-LGS, Medtronic) or stopping the infusion when a hypoglycemia is predicted in the 30 min (PREDICTIVE, Medtronic 640G). There is a new model that has an algorithm for the basal rate and corrects for hyper- or hypoglycemia automatically (Medtronic 670G).

Initial Settings

Initial Total and Basal Insulin Dose

Initial *total daily insulin dose (TDD)* may be calculated (Fig. 38.1):

– With the patient's weight (0.5 × patient's weight in kg or 0.23 × patient's weight in lb)
– Making and adjustment (usually a 25% reduction, if A1c is in target) to his previous total insulin regimen by multiple daily injection (MDI)
– Or a mix of both approaches using the average

Then, 50% of that dose is used as the *total daily basal dose* and can be divided equally in 24 h (IU/h).

In addition, if a patient has been reasonably well controlled on MDI, on a basal-bolus regimen, one could do the conversion from the total basal insulin analogue dose to the *total daily basal dose*, by reducing it by 5–25%. It must be pointed out that when converting from glargine insulin to CSII, one must reduce the dose at least 20%. When converting from degludec insulin to CSII, the reduction may be lower (5–15%).

The basal dose may be set in the pump configuration in insulin IU hour by hour, and some devices may have the possibility to set different basal rates at each 30-min interval.

– When initiating the basal rate, one can initiate with a constant basal rate per hour for the 24 h, for example, 0.5 IU per hour, or with different basal rates for different time frames, depending if it is known that the patient presents dawn phenomenon (higher rate) or early morning hypoglycemia (lower rate).
– Insulin pumps may have the possibility to configure different basal patterns, for example, a higher one for sick days and a lower one for exercise days.

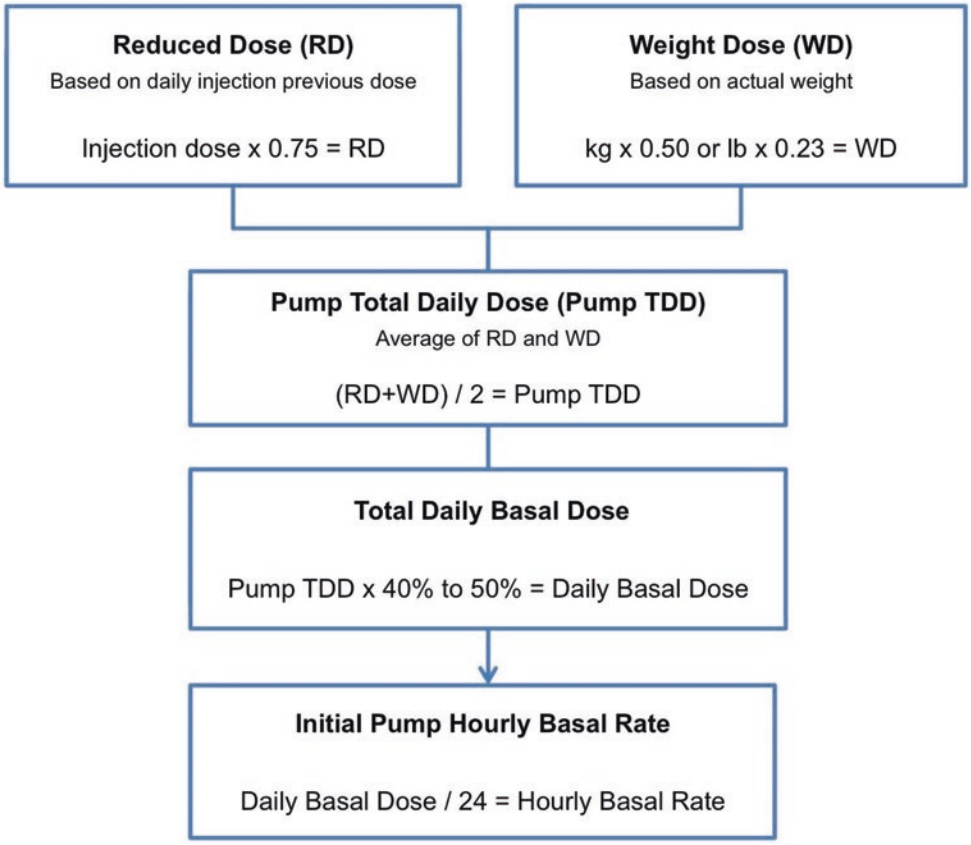

Fig. 38.1 Initial pump hourly basal rate. (Adapted from medtronic protocol [3])

– Another function of CSII devices is to set temporary basal rates anytime, with durations from 30 min to 24 h. Temporal basal infusion may be programed by insulin units or by percentage. For example, if the patient has an unplanned physical activity, he can set a basal reduction of "X%" during "X" hours.

Initial Bolus Calculation

Initial bolus calculation settings include the following:

– *Insulin-to-carb ratio (ICR):* This means how many grams of carbohydrate will be covered by the infusion of one unit of fast-acting insulin. For optimal control, a patient may need different ICRs during the day. *If a patient on multiple daily injections has established an ICR that provides reasonable post-prandial glucose control, the pump therapy settings can be done using that ICR. If a patient is not yet carb counting or does not have an accurate food log, use the 450 Rule (450/total daily dose)* (Fig. 38.2) [3].
– *Insulin* sensitivity *factor (ISF)***:** This factor indicates the mg/dL or mmol/L of BG that is lowered by the infusion of one unit of fast-acting insulin. *If a patient on multiple daily injections has an established ISF that currently provides reasonable correction doses, the pump therapy settings can be started using that ISF. For patients who have frequent hypoglycemia or hypoglycemia unawareness, use the 2000 Rule (2000/TDD)* (Fig. 38.3) [3]. Please refer to Chap. 37, for more details on these calculations.

Fig. 38.2 Initial insulin-to-carb ratio (ICR) [3]

Fig. 38.3 Initial insulin sensitivity factor (ISF). (Adapted from [3])

– *Active* insulin *(AI):* Some devices include a bolus calculator feature that also considers the active insulin from a previous bolus and estimates the adjustment to reduce the hypoglycemia risk. In order to program that, the settings should include active insulin in hours. *The length of time fast-acting insulin lowers the blood glucose level varies in each individual. Usually, it can be set from 3 to 5 h* [3].
– *Blood glucose target range (BGTR):* This is the range of BG levels that we want the patient to achieve. With this information, the bolus calculator feature will determine if a correction is needed. *When determining target ranges, keep in mind, these are not the same as ADA or AACE BG guidelines; instead, they are the values the pump "targets" when correcting high or low BGs and should be individualized, especially, in patients with history of severe hypoglycemia or hypoglycemia unawareness* [3].
– *Insulin bolus delivery* can be done in three different ways:
  Normal bolus: The total bolus estimation is delivered at that moment.
  Square wave bolus: The total bolus estimation is delivered during a lapse of time defined by the patient. It can be anywhere from 30 min to 8 h, for example. It is usually used when consuming food high in fat and protein.
  Dual wave bolus: This bolus is a mix between the normal and the square wave bolus. The patient can set a percentage of the bolus to be given now (normal) and a percentage of the bolus to be given over a lapse of time (square wave bolus). This type of bolus can be used for meals high in carbohydrate, fat, and protein, such as pizza.

Adjustments Step by Step

Here is a step by step example of fine-tuning adjustments:

Step 1. Calculate initial doses

Total daily dose, basal hourly rate (Fig. 38.4), ICR (Fig. 38.5), and ISF (Fig. 38.6)

Step 2 Patient's BG registry

Usually, the information regarding BG levels, carbs ingested, insulin boluses, and exercise can be entered in the insulin pump. But, sometimes, many patients forget to enter BG levels and carbs during a hypoglycemia event, and that information is lost when downloading the insulin pump information in the computer. If a hypoglycemia is not recorded, then when making adjustments, important information will be omitted. For that reason and for educational purposes, it is recommended that patients will make their own manual BG registry log (Figs. 38.7, 38.8, and 38.9). When a person does his own BG registry manually, he is more conscious of his own decisions, which can promote engagement.

Suggested BG registry format:

Step 3 Basal rate fine-tuning

Although some patients may achieve good BG control using one constant basal rate, most will need different basal rates during the day to achieve a tight BG control. Once the initial doses are set, the healthcare team should help the patient to evaluate and fine-tune the basal rate. There are some guidelines to follow during the evaluation period [4].

- The first time-frame to be evaluated should be overnight.
- It is preferred to see similar results for 2 days in a row to consider it a pattern and make adjustments. If the blood glucose is dropping during the evaluation, you can consider to change the rate without confirming a pattern.
- The blood glucose should be 100–150 mg/day (5.5–8.3 mmol/L) before starting the evaluation.
- On the day of the evaluation, the patient should avoid exercising, eating high fat meals, or drinking alcohol. Do not plan an evaluation if the patient is sick, under unusual stress, or if the patient experienced a severe hypoglycemia that day.
- The last meal before the beginning of the evaluation should be easy to count, preferably with low fat foods.
- Stop the evaluation if the blood glucose drops or rises out of the target range and treat it.
- Basal evaluation should begin 3–5 h after the last bolus.
- Check blood glucose every 1–2 h. For the overnight time frame: before bedtime, midnight, between 2–3 a.m., and upon awakening.

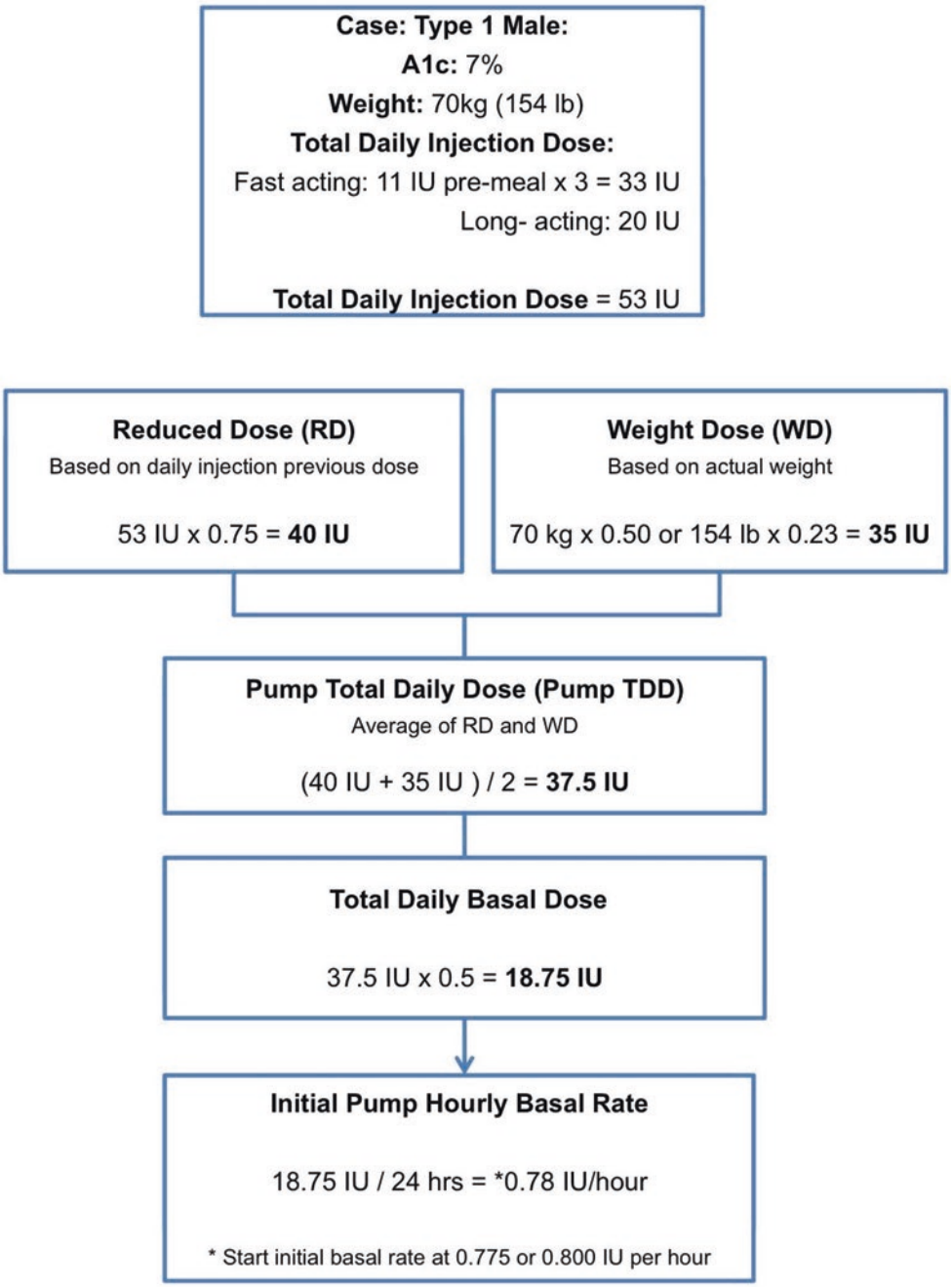

Fig. 38.4 Initial basal hourly rate doses calculation example. (Adapted from [3])

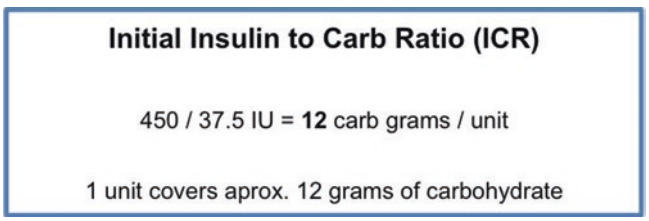

Fig. 38.5 Initial ICR calculation example. (Adapted from [3])

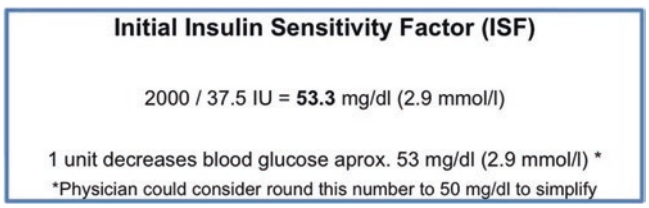

Fig. 38.6 Initial ISF calculation example. (Adapted from [3])

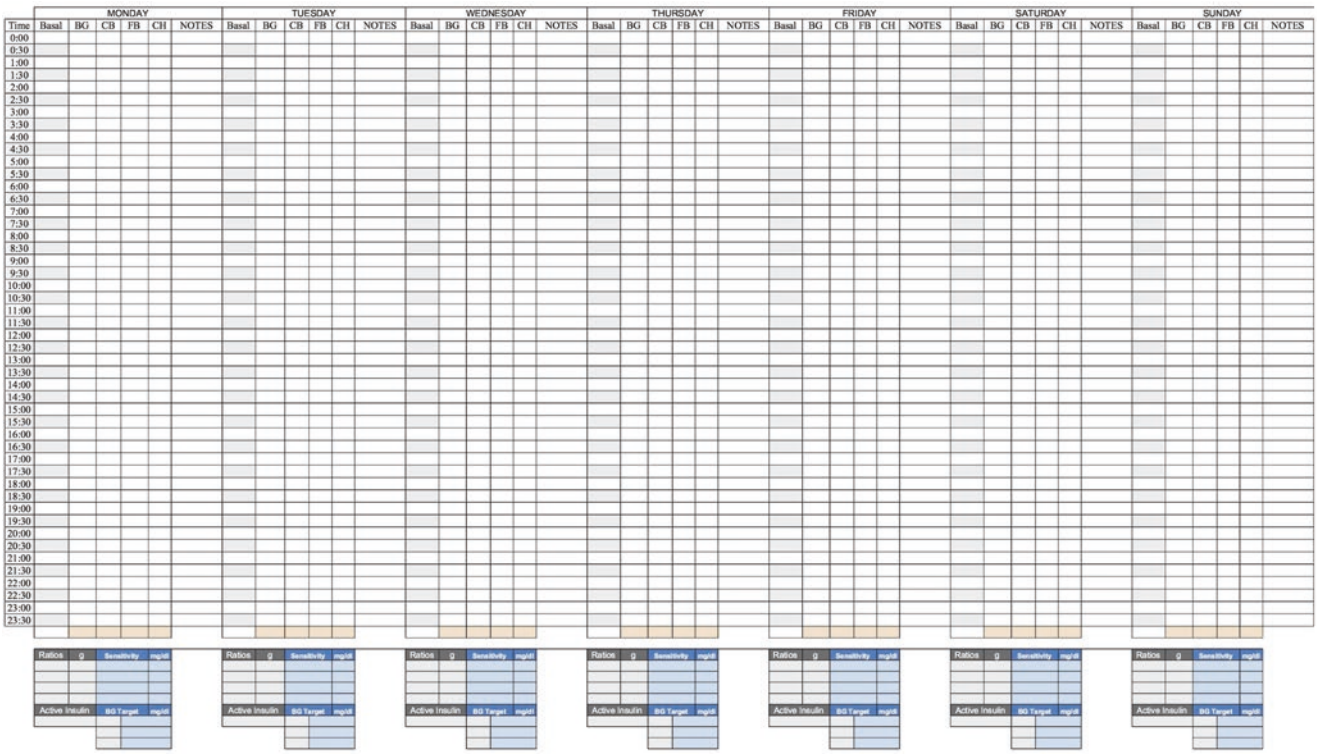

Fig. 38.7 Example of BG registry format. (Faradji R, Sainz E, Clinica EnDi, unpublished)

Time frame/guidelines	Check blood glucose	Evaluation
Overnight Eat dinner earlier: easy to count, low fat Don't eat afterward	• 3 h after dinner bolus • Midnight • 3:00 a.m. • Upon awakening	Basal rates are correct if BG does not increase or decrease more than 30–40 mg/dL (1.7 a 2.2 mmol/L) during the evaluation period If BG increases, basal rate needs to be increased for this time period If BG decreases, basal rate needs to be decreased for this time period
Breakfast time Check your BG upon awakening If BG is between 100–150 mg/dL (5.5–8.5 mmol/L) approximately begin evaluation Skip breakfast Eat no food until noon	Every 1–2 h until noon/ lunch time	
Lunch time Eat breakfast at usual time: easy to count, low fat Skip lunch Eat no food until dinner	• 3 h After breakfast bolus • Every 1–2 h until dinner	
Dinner time Eat lunch at usual time: Easy to count, low fat Skip dinner Eat no food until bedtime Eat a late dinner or bedtime snack if you desire	• 3 h. After lunch bolus • Every 1–2 h until bedtime snack/late dinner	
• Consider that meal time frames are different in different cultures; maybe you will have to adjust these guidelines • Each time frame evaluation must be done on different days • Keep in mind that basal insulin delivered has its maximum effect 2–3 h later. For example, if blood glucose is elevated at 3:00 in the morning, the basal rate must be changed starting at 0:00 h		

Adapted from [4]

Basal rate fine-tuning step-by-step didactic example (Fig. 38.10).

Day 1 Basal evaluation overnight: Monday to Tuesday
18:00 h—BG before dinner—120 mg/dL (6.7 mmol/L).
22:00 h—BG 4 h after dinner—150 mg/dL (8.3 mmol/L).
00:00 h—BG midnight—170 mg/dL (9.4 mmol/L).
03:00 h—BG 3 am- 240 mg/dL (13.3 mmol/L).

BG rises more than 30–40 mg/dL (2 mmol/L approx.) from midnight to 3:00 h. The patient should adjust basal rate from 0.800 to 0.850 IU/h on that time frame.

Day 2 Basal evaluation overnight: Tuesday to Wednesday
18:00 h—BG before dinner—110 mg/dL (6.1 mmol/L).
22:00 h—BG 4 h after dinner—155 mg/dL (8.6 mmol/L).

BG – Blood glucose (mg/dl)
CB – Correction Bolus (insulin units)
FB – Food Bolus (insulin units)
CH – Carbohydrates (grams)
NOTES – Food detail, excercise, cannula change, etc.

	MONDAY					
Time	Basal	BG	CB	FB	CH	NOTES
0:00	**0.800**					
0:30						
1:00	0.800					
1:30						
2:00	0.800					
2:30						
3:00	0.800					
3:30						
4:00	0.800					
4:30						
5:00	0.800					
5:30						
6:00	0.800	200	2	2.5	30	bread
6:30						
7:00	0.800					
7:30						
8:00	0.800					
8:30						
9:00	0.800	160	1.2			
9:30						

Fig. 38.8 Detailed example BG Registry Format. (Faradji R, Sainz E, Clinica EnDi, unpublished)

Ratios	g	Sensitivity	mg/dl
0:00	12	0:00	50
Active Insulin		**BG Target**	**mg/dl**
3 hrs		0:00	100-110
		6:00	90-100
		20:00	100-110

Fig. 38.9 Detailed example of pump settings summary

00:00 h—BG midnight—170 mg/dL (9.4 mmol/L).
03:00 h—BG 3 am—210 mg/dL (11.6 mmol/L).

BG rises more than 30–40 mg/dL (2 mmol/L approx.) from midnight to 3:00 h, even with the last adjustment, patient could adjust basal rate from 0.850 to 0.900 IU/h on that time frame.

We also observe a 2-day pattern of BG rising moderately from 22:00 to 00:00 h. The patient and his healthcare team could consider adjusting the basal rate from 0.800 to 0.850 u/h on that time frame.

Day 3 Basal evaluation overnight: Wednesday to Thursday
18:00 h—BG before dinner—120 mg/dL (6.7 mmol/L).
22:00 h—BG 4 h after dinner—155 mg/dL (8.6 mmol/L).
00:00 h—BG midnight—130 mg/dL (7.2 mmol/L).
03:00 h—BG 3 am—120 mg/dL (6.7 mmol/L).
06:00 h—BG wakeup—110 mg/dL (6.1 mmol/L).

BG remained without big changes during the night.

We can observe another pattern during the day on days 1, 2, and 3: from 9:00 h to 12:00 h BG decreases more than 30-40 mg/dL (2 mmol/L approx.): The patient could consider decreasing the basal rate from 0.800 to 0.750 IU/h during that time frame.

Day 4 Basal evaluation morning and overnight: Thursday morning and Thursday to Friday

Thursday morning:
09:00 h—BG 3 h after breakfast 160 mg/dL (8.9 mmol/L).
12:00 h—BG 3 h before lunch 150 mg/dL (8.3 mmol/L).

BG remained without big changes during the morning, the basal reduction to 0.750 u/h worked. After analyzing the breakfast postprandial results, the patient with his healthcare team could consider adjusting the breakfast ICR in order to achieve a better postprandial glucose result from 12 g of carbs to 10 g of carbs per 1 unit of insulin, just for breakfast.

Thursday to Friday:
18:00 h—BG before dinner—110 mg/dL (6.1 mmol/L).
20:00 h—BG 2 h after dinner—170 mg/dL (9.4 mmol/L).
23.00 h—BG 5 h after Dinner—120 mg/dL(6.7 mmol/L)
03:00 h—BG 3 a.m.—110 mg/dL (6.1 mmol/L).
06:00 h—BG wakeup—110 mg/dL (6.1 mmol/L).

BG remained without big changes during that night. We already have 2 days without big changes overnight. For now, overnight basal rate is working as expected.

Day 5 Bolus breakfast ratio evaluation: Friday.
06:00 h—BG before breakfast—110 mg/dL (6.1 mmol/L).
09:00 h—BG 3 h after breakfast—120 mg/dL (6.7 mmol/L).
12:00 h—BG before lunch—90 mg/dL (5 mmol/L).

BG remained without big changes during the morning. After breakfast, postprandial BG result is on a better range, without big changes and without hypoglycemia until lunch.

	DAY 1 MONDAY						DAY 2 TUESDAY					
Time	Basal	BG	CB	FB	CH	NOTES	Basal	BG	CB	FB	CH	NOTES
0:00	**0.800**						**0.800**	170				
0:30												
1:00	0.800						0.800					
1:30												
2:00	0.800						0.800					
2:30												
3:00	0.800						0.800	240	2.6			
3:30												
4:00	0.800						0.800					
4:30												
5:00	0.800						0.800					
5:30												
6:00	0.800	200	2	2.5	30	bread	0.800	120	0.4	2.5	30	bread
6:30						coffee						coffee
7:00	0.800						0.800					
7:30												
8:00	0.800						0.800					
8:30												
9:00	0.800	180	1.2				0.800	190				
9:30												
10:00	0.800						0.800					
10:30												
11:00	0.800						0.800					
11:30												
12:00	0.800	60		3.7	55	sandwich	0.800	70		3.7	45	sandwich
12:30						fruit						fruit
13:00	0.800						0.800					
13:30												
14:00	0.800						0.800					
14:30												
15:00	0.800						0.800					
15:30												
16:00	0.800						0.800					
16:30												
17:00	0.800						0.800					
17:30												
18:00	0.800	120	0.4	5	60	pasta	0.800	110	0.2	5	60	rice
18:30						salad						chicken
19:00	0.800						0.800					
19:30												
20:00	0.800						0.800					
20:30												
21:00	0.800	150					0.800	155				
21:30												
22:00	0.800						0.800					
22:30												
23:00	0.800						0.800					
23:30												
	19.2						19.2					

	DAY 3 WEDNESDAY						DAY 4 THURSDAY						DAY 5 FRIDAY					
Time	Basal	BG	CB	FB	CH	NOTES	Basal	BG	CB	FB	CH	NOTES	Basal	BG	CB	FB	CH	NOTES
0:00	**0.850**	170					**0.900**	130					**0.900**					
0:30																		
1:00	0.850						0.900						0.900					
1:30																		
2:00	0.850						0.900						0.900					
2:30																		
3:00	0.850	210	2				0.900	120					0.900	110				
3:30																		
4:00	0.800						0.800						0.800					
4:30																		
5:00	0.800						0.800						0.800					
5:30																		
6:00	0.800	100		2.5	30	bread	0.800	110		2.5	30	bread	0.800	110		3	30	bread
6:30						coffee						coffee						coffee
7:00	0.800						0.800						0.800					
7:30																		
8:00	0.800						0.800						0.800					
8:30																		
9:00	0.800	170					0.750	160					0.750	120				
9:30																		
10:00	0.800						0.750						0.750					
10:30																		
11:00	0.800						0.750						0.750					
11:30																		
12:00	0.800	50		3.7	50	sandwich	0.800	150	1	3.7	45	sandwich	0.800	90		3.7	45	sandwich
12:30						fruit						fruit						fruit
13:00	0.800						0.800						0.800					
13:30																		
14:00	0.800						0.800						0.800					
14:30																		
15:00	0.800						0.800						0.800	120				
15:30																		
16:00	0.800						0.800						0.800					
16:30																		
17:00	0.800						0.800						0.800					
17:30																		
18:00	0.800	120	0.4	5	60	pasta	0.800	110	0.2	5	60	rice	0.800	90		5	60	rice
18:30						salad						chicken						meat ball
19:00	0.800						0.800						0.800					
19:30																		
20:00	0.800						0.800	170					0.800	160				
20:30																		
21:00	0.850	155					0.850						0.850					
21:30																		
22:00	0.850						0.850						0.850					
22:30																		
23:00	0.850						0.850	120					0.850	110				
23:30																		
	19.55						19.6						19.6					

	Ratios	g	Sensitivity	mg/dl	Active Insulin	BG Target	mg/dl
DAY 1	0:00	12	0:00	50	3 hrs	0:00	100-110
						6:00	90-100
						20:00	100-110
DAY 2	0:00	12	0:00	50	3 hrs	0:00	100-110
						6:00	90-100
						20:00	100-110
DAY 3	0:00	12	0:00	50	3 hrs	0:00	100-110
						6:00	90-100
						20:00	100-110
DAY 4	0:00	12	0:00	50	3 hrs	0:00	100-110
						6:00	90-100
						20:00	100-110
DAY 5	0:00	12	0:00	50	3 hrs	0:00	100-110
	6:00	10				6:00	90-100
	12:00	12				20:00	100-110

Fig. 38.10 Didactic sample of BG Registry: days 1–5

Step 4 Insulin-to-carb ratio (ICR) fine-tuning.

Once the basal rate has been evaluated and adjusted, we can continue with ICR and insulin sensitivity factor (ISF) evaluation and adjustments. There are some recommendations:

- ICR evaluation should take place when BG before a meal is in target. If the user needs to add a correction bolus to get the BG down, it won't be the best time to evaluate the ICR.
- The person must choose a low-fat meal, moderate in carbs (30–45 g) and prefer a meal that is easy to count.
- The person should estimate the carbs, apply the food bolus according to the pump settings, and eat.
- Then, the user should check his BG every 1–2 h for the next 4 h after that meal.
- Four to five hours after the meal, the BG should return to the target range, if the ICR is correct.
- It is recommended to reevaluate the ICR on different days and at different times of the day.
- Consider that the ICR can be different for different times of the day.

An example can be seen on days 4 and 5 as explained before.

Step 5 Sensitivity factor (ISF) fine-tuning.

Usually, the insulin sensitivity factor (ISF) evaluation occurs naturally when we observe on the patient BG registry log book, an isolated correction bolus. This correction bolus should have no food, exercise, or other interfering factors at that time. We can then manually calculate how many mg/dL

or mmol/L the BG drops with the bolus infusion of one unit of insulin.

The insulin pump user can identify an opportunity to evaluate his own ISF when he needs to take a correction bolus, and at least 3 h have passed since his last food bolus. The person must take a correction bolus based on his pump settings and then check his BG after 2 h and then again at 3–4 h without eating during that time frame.

ISF fine-tuning, step-by-step didactic example (Fig. 38.11).

Day 6 Sensitivity factor evaluation. Saturday morning.

7:00 h—BG wake up—220 mg/dL (12.2 mmol/L)—2.2u insulin correction bolus according to the pump settings: target BG 110 mg/dL (6.1 mmol/L) and ISF 50 mg/dL (2.7 mmol/L).

9:00 h—BG 90 mg/dL (5 mmol/L).

10:00 h—BG 3 h after correction bolus—65 mg/dL (3.6 mmol/L).

We can estimate the adjusted sensitivity factor based on the evaluation results as follows (Figs. 38.12 and 38.13):

As we can see, even though the ISF is 50 mg/dL (2.7 mmol/L), the BG drops 70 mg/dL (3.8 mmol/L). Therefore, we can adjust the ISF to 70 mg/dL (3.8 mmol/L), in that time frame.

Keep in mind that the ISF can be different on different time frames during the day. Usually, a patient may need an ISF for the night and another one during the day.

Comparison of initial pump settings with pump settings after fine tuning adjustments

Initial pump settings	Pump settings after first adjustments
Basal rate From 00:00 to 24:00 h—0.800 IU/h Total basal insulin: 19.2 units *Bolus ratios (ICR):* From 00:00 to 24:00 h—12 g *ISF:* From 00:00 to 24:00 h—50 mg/dL	*Basal rate* From 00:00 to 03:00 h- 0.900 IU/h From 03:00 to 09:00 h- 0.800 IU/h From 09:00 to 12:00 h- 0.750 IU/h From 12:00 to 21:00 h- 0.800 IU/h From 21:00 to 24:00 h- 0.850 IU/h Total basal insulin: 19.6 units *Bolus ratios (ICR):* From 00:00 to 06:00 h—12 g From 06:00 to 12:00 h—10 g From 12:00 to 24:00 h—12 g *ISF:* From 00:00 to 11:00 h—70 mg/dL (2.7 mmol/L) From 11:00 to 24:00 h—50 mg/dL (3.8 mmol/L)

DAY 6 — SATURDAY

Time	Basal	BG	CB	FB	CH	NOTES
0:00	**0.900**	110		2.5	30	party
0:30						dessert
1:00	0.900					
1:30						
2:00	0.900					
2:30						
3:00	0.900					
3:30						
4:00	**0.800**					
4:30						
5:00	0.800					
5:30						
6:00	0.800					
6:30						
7:00	0.800	220	2.2			
7:30						
8:00	0.800					
8:30						
9:00	**0.750**	90				
9:30						
10:00	0.750	65		3	35	bread
10:30						coffee
11:00	0.750					
11:30						
12:00	**0.800**	150	1	3.7	45	sandwich
12:30						fruit
13:00	0.800					
13:30						
14:00	0.800					
14:30						
15:00	0.800	140				
15:30						
16:00	0.800					
16:30						
17:00	0.800					
17:30						
18:00	0.800	120	0.2	3.7	45	bread
18:30						chicken
19:00	0.800					
19:30						
20:00	0.800					
20:30						
21:00	**0.850**	150				
21:30						
22:00	0.850					
22:30						
23:00	0.850					
23:30						
	19.6					

Ratios	g	Sensitivity	mg/dl
0:00	12	0:00	50
6:00	10		
12:00	12		

Active Insulin	BG Target	mg/dl
3 hrs	0:00	100-110
	6:00	90-100
	20:00	100-110

DAY 7 — SUNDAY

Time	Basal	BG	CB	FB	CH	NOTES
0:00	**0.900**					
0:30						
1:00	0.900					
1:30						
2:00	0.900					
2:30						
3:00	0.900					
3:30						
4:00	**0.800**					
4:30						
5:00	0.800					
5:30						
6:00	0.800	90		3	30	bread
6:30						coffee
7:00	0.800					
7:30						
8:00	0.800					
8:30						
9:00	**0.750**	120				
9:30						
10:00	0.750					
10:30						
11:00	0.750					
11:30						
12:00	**0.800**	100		3.7	45	sandwich
12:30						fruit
13:00	0.800					
13:30						
14:00	0.800					
14:30						
15:00	0.800	150				
15:30						
16:00	0.800					
16:30						
17:00	0.800					
17:30						
18:00	0.800	130	0.2	5	60	rice
18:30						chicken
19:00	0.800					
19:30						
20:00	0.800					
20:30						
21:00	**0.850**	160				
21:30						
22:00	0.850					
22:30						
23:00	0.850					
23:30						
	19.6					

Ratios	g	Sensitivity	mg/dl
0:00	12	0:00	50
6:00	10		
12:00	12		

Active Insulin	BG Target	mg/dl
3 hrs	0:00	100-110
	6:00	90-100
	20:00	100-110

Fig. 38.11 Didactic sample of BG Registry: days 6 and 7

$$\frac{\text{initial BG - final BG*}}{\text{correction bolus}} = \text{ISF}$$

*BG 3 to 4 hours after correction bolus

Fig. 38.12 ISF estimation based on BG registry results

$$\frac{220 - 65}{2.2\ \text{IU}} = 70\ \text{mg/dl}$$

Fig. 38.13 ISF estimation based on the results of a didactic example

Special Situations

Exercise

The normal physiologic response to exercise is the reduction in insulin production and the increase in the secretion of glucagon and sympathetic hormones, as well as other counterregulatory hormones [5–7].

The response to exercise is different depending on the type of exercise:

- Anaerobic exercise (weights, high intensity sprints): There is more catecholamine secretion and therefore increased likelihood in BG rise.
- Aerobic (running, swimming, biking): There is more energy expenditure, and therefore, the risk of hypoglycemia is higher.

In a person living with T1D, where insulin administration is exogenous and subcutaneous, insulin secretion cannot be decreased. In addition, the increase in glucagon associated with exercise may be lost in the first few years after diagnosis. Finally, if the patient has autonomic insufficiency (either organic or because of hypoglycemia associated autonomic failure-HAAF), the sympathetic response will be attenuated, leaving the person at risk of severe hypoglycemia and hypoglycemia unaware. As explained in Chap. 51, exercise can worsen this situation [5–7].

The risk of hypoglycemia is not only present during exercise but also in the hours following it, because of muscle glycogen stores replenishment that normally occur after exercise. This phenomenon can occur 7 h after doing exercise and may last for up to 24 h [8–10]. If exercise is performed on a daily basis, insulin sensitivity increases, and the insulin requirements may decrease.

In a patient with T1D, three responses to exercise may occur, depending on the insulin concentrations and on the level of the counterregulatory hormones [5–7].

(a) Euglycemia: If circulating insulin is decreased prior to exercise and the response to catecholamines is adequate, there will be appropriate glucose utilization by the muscle.
(b) Hypoglycemia: If there is excess or normal insulin concentrations and a normal or attenuated catecholamine response, the habitual response will be hypoglycemia.
(c) Hyperglycemia: This can occur in patients with uncontrolled diabetes, or in patients with good control, if there is relative insulin deficiency.

If there is insulin deficiency and an excessive catecholamine response, there can be the development of diabetic ketoacidosis.

In those patients treated with CSII, several studies have been carried out to evaluate what to do when exercising and using the pump.

Dr. Moshe Phillip's group published a study in 2005 [11], where the use of the insulin pump at a basal rate of 50% was compared to insulin pump disconnection during exercise in ten kids. There was no significant difference in the rate of hypoglycemia during exercise in the two groups, but there was an increased risk of hypoglycemia several hours after exercise in both groups. A trend toward more hypoglycemia several hours after exercise was seen in the group that used the temporary basal rate, compared to those that disconnected. Their recommendation is to disconnect the pump during exercise and to check BG levels frequently during and after exercise.

DirecNet (2006) [12] studied 49 children, where insulin pump use or not was compared during exercise at 4:00 p.m. They found that hypoglycemia during exercise was lower in the group that disconnected (16 vs. 43%), but post-exercise hyperglycemia was higher (27 vs. 4%).

Dr. Ana María Gomez published a study in 2015 [9], where the effect of exercise in BG levels was compared in exercise performed at the fasting state versus exercise performed 4 h after the main meal, in 35 insulin pump adult users. Both groups did aerobic exercise for 1 h, in a running machine. The insulin pump was disconnected immediately before, during and 45 min after finishing the exercise. They found that if exercise is performed in the morning, the rate of hypoglycemia is lower than if performed in the afternoon. Most hypoglycemic events occurred 15–24 h post-exercise. Those patients that performed fasting exercise increased 20% their euglycemia time, the day after exercise. They concluded that early morning exercise decreases the rate of hypoglycemia and improves glucose control.

McAuley et al. in 2016 [13] studied the effect of using a temporary basal rate of 50% 1 h before and during exercise (30 min), versus rest in 14 adult subjects with T1D. They found that even with the basal rate reduction, insulin concentrations rise during exercise, compared to being at rest. Three of the 14 subjects presented hypoglycemia, even with the temporary basal rate reduction, and required supplemental carbohydrates. Their recommendation is to give supplementary carbohydrates to those patients with BG levels below 126 mg/dL (7 mmol) and to consider basal rate reductions higher than 50% before and during exercise.

Strategies to decrease hypoglycemia during and after exercise in insulin pump users include the following [14]:

1. Having supplementary carbohydrates before exercise
2. Reducing basal rate before and during exercise (50% or more)
3. Consider disconnecting insulin pump during and 45 min after exercise
4. Reducing meal bolus if exercise will occur 2 or 3 h after exercise
5. Reducing basal rate post exercise, to decrease the incidence of late hypoglycemia or nocturnal hypoglycemia (e.g., a 20% reduction, i.e., an 80% basal rate, during the night of the exercise day)
6. Reducing meal bolus after dinner, to reduce the incidence of late hypoglycemia or nocturnal hypoglycemia
7. Performing high resistance and intensity exercise prior and after aerobic exercise
8. Using CGM to help guide insulin doses and additional carbohydrate intake.

Each patient will need to study his own response to exercise and to the different types of exercise so that he can make the best decisions, together with his healthcare team, to try to prevent exercise-induced hypoglycemia.

Sick Days

It is important that the patient and the healthcare team have a set plan in case of sick days. The patient should understand that during sick days his BG levels may rise, even if he is not eating as much, because of the counterregulatory hormones. For that reason, he must maintain well hydrated, check his BG levels often, and give himself a correction bolus when needed. He also needs to have urine or glucose ketone test strips and check if the BG is higher than 240 mg/dL (13.3 mmol/L). If positive, he should contact the healthcare team.

In addition, if the BG levels remain higher than normal, he may need to set a temporarily basal rate such as 120–150% for several hours during the day and the reassess.

The patient must understand that if the BG is higher than 240 mg/dL (13.3 mmol/L) in two occasions in a row, even if he has given himself a correction bolus, he must do the following:

1. Check ketones
2. Look for a possible cause (i.e., cannula occlusion or dislodgement, insulin bubbles in the catheter, spoiled insulin)
3. Correct with an insulin injection (with insulin syringe or pen)
4. Change the insulin, insulin reservoir, and infusion set

Patients should be trained to always carry with themselves an extra infusion set change and an insulin delivery device like insulin pen or syringes and an insulin vial.

In case there are ketones present, the patient will need to increase his correction dose. He may need up to 15–20% of his total insulin daily dose as correction and check BG and ketones in 1 h.

Another important consideration is that sometimes the patient will be prescribed corticosteroids, as part of the treatment of his inter-current disease (i.e., asthma attack, vestibular neuronitis, etc.). In that case, BG levels will rise significantly around 6 h after the initial dose. He must keep well hydrated and check BG often, and he must make insulin adjustments as needed. He may need a temporary basal rate of 150% or more and may need to change the ICR and ISF to as much as 1:5 g and 1:15 mg/dL (~1:1 mmol/L), respectively.

Finally, if there is nausea and vomiting that cannot be treated with an antiemetic at home, regardless if there are or not ketones present, the patient should be seen in the emergency room for hydration, anti-emetic treatment, and diagnosis of the cause of the nausea and vomiting. He may need to be hospitalized.

Fasting

If a patient living with T1D has his basal rate set correctly, fasting should not be a problem. If it is set too high, he may then be at risk of hypoglycemia. To know if a basal rate is set correctly, a basal rate evaluation can be performed as explained above.

Fasting may be required before medical or surgical procedures or may be a personal or religious choice (such as in Yom Kippur or in Ramadan) [15]. Careful monitoring of glucose levels (either capillary, flash or continuous), avoiding bolus insulin, or if needed, correcting to a higher BGTR (150 mg/dL—approx. 8 mmol/L instead of 100 mg/dL- approx. 5.5 mmol/L) and temporary reductions in basal insulin may be required to maintain safe glucose levels.

Hospitalizations

T1D patients using an insulin pump, who are conscious, should be able to maintain the use of their pump while in the hospital [1, 2], especially if they have not been admitted for an acute hypo or hyperglycemic crisis. Ideally, their specialist in insulin pump therapy should be consulted during their hospital stay.

With the increased utilization of insulin pumps by patients, hospitals should be encouraged to have pump experts on staff, especially the anesthesiologists and the ward physicians. As stated in the American Diabetes Association's 2014 Standards of Medical Care [16], "Patients who use CSII pump therapy in the outpatient setting can be candidates for diabetes self-management in the hospital, provided that they have the mental and physical capacity to do so. [The] availability of hospital personnel with expertise in CSII therapy is essential. It is important that nursing personnel document basal rates and bolus doses on a regular basis (at least daily)."

It is important to note that if going to an MRI machine, the pump should be disconnected, and the sensor should be removed during the study.

Surgery [1, 2, 15]

During surgery two key situations occur:

1. The patient is fasting and therefore is at risk of hypoglycemia.
2. The increase in stress hormones from surgery could raise BG levels.

For these reasons, it is important to monitor BG levels before surgery, every hour during surgery and recovery room, and every 3 h while fasting.

For the most part, patients should be able to continue using their insulin pump during surgery. It is important to note the localization of the cannula (and the sensor, if in place) and to avoid dislodging them.

Since the patient will be anesthetized, it is important to have someone that knows how to manage the pump during that time. It could either be the anesthesiologist, the insulin pump therapy specialist (endocrinologist or registered nurse/diabetes educator) or, if not possible and if allowed in the operating room, a family member (i.e., spouse or parent), who knows how to operate the pump and is in contact with the insulin pump specialist.

During surgery, a temporary basal rate may be required, either a lower rate to prevent hypoglycemia, or a higher rate if BG levels start to rise secondary to the stress. Also, correction bolus may be given to a target BG level of around 150 mg/dL (approx. 8 mmol/L).

It is not recommended, but if decided by the medical team, the insulin pump could be stopped, and an intravenous insulin infusion should be initiated.

Menstruation [15]

For some women living with T1D, important changes occur during the menstrual cycle. During the premenstrual period, they may experience higher BG levels and increased insulin requirements. In addition, when menstruation starts and progesterone concentrations fall steeply, insulin requirements may fall sharply, and there may be a higher risk of hypoglycemia. For these reasons, different basal rate patterns could be set in the insulin pump for these situations. Or a temporary basal rate could be set.

Some women will report increased insulin requirements when using birth control pills; therefore, insulin dose adjustments will need to be made.

Pregnancy [1, 15]

CSII has not yet proven to be superior to MDI for BG control and pregnancy outcomes (macrosomia). A large randomized control trial is necessary to study this. Even then, CSII facilitates BG control on those patients that are already on it when getting pregnant. And on those that are on MDI and are not well controlled, they can be changed to CSII to improve their BG control.

Pregnancy is a state where several changes occur, and one must be familiarized with them, to optimally control BG levels during each trimester.

If teratogenicity occurs, this will occur in the *first 8 weeks of gestation*; therefore, it is very important to have the best possible BG control preconception, with a HbA1c target of <6%, if possible. After words, if there is poor glycemic control, the risk is macrosomia, due to glucose passage through the placenta, and increase in insulin secretion by the fetus. If the BG levels are elevated during delivery, the risk is of neonatal hypoglycemia.

In the *first trimester*, there is an estate of increased insulin sensitivity, and the normal BG levels range from 60–90 mg/dL, and the post-prandial levels are usually below 120 mg/dL. In this trimester, the risk of hypoglycemia increases due to the nausea and vomiting. During this phase, using temporary basal rates, or doing basal insulin adjustments if a pattern is seen, can be easily done with insulin pump therapy. In addition, giving the insulin bolus after eating can be especially useful if nausea and vomiting are occurring frequently.

In addition, pregnancy is a state of accelerated ketosis [17]; just a few hours of insulin interruption can lead to hyperglycemia and ketosis. Therefore, the patient must be extremely careful with insulin infusion site changes.

During the *second trimester*, the insulin requirements slowly start to increase.

After the second trimester, as the abdominal wall starts stretching and the subcutaneous space starts to thin out, special care should be taken with choosing the insulin infusion sites; the arms and thigh can be an option.

After the 24th week (*third trimester*), there is an increase in human placental lactogen and other counterregulatory hormones, leading to a significant increase in insulin requirements that can occur even twice per week. These can occur up until the 36th week. Using an insulin pump can facilitate doing the changes twice a week.

During labor, there is significant glucose utilization by the uterine muscular contractions that is comparable to intense exercise (2.55 mg/kg/min); therefore, an intravenous infusion of 10% glucose will be required at 100 cc/h. Usually, the basal rate is left constant.

Right after the placental delivery, the insulin requirements fall significantly, leading to risk of hypoglycemia for the next 48 h. In these time, the patient will:

1. Stop the pump until BG levels are above 100 mg/dL (5.5 mmol/L)
2. Require to return to the pre-gestational insulin pump settings
3. May not require insulin meal bolus
4. Require the infusion of dextrose at 5% with normal saline at 100 cc/h

In case of a *cesarean section*, the BG levels may temporarily increase due to the surgical stress, and the basal rate should be temporarily increased.

During *breastfeeding*, insulin requirements fall significantly (by up to 25%), as available carbohydrate is used to provide lactose in milk. This, added to the post-delivery decreased insulin requirements, can increase the risk of hypoglycemia. At the beginning, the patient can take 15 g of carbohydrates before lactation and can also use temporary basal rates to reduce the risk of hypoglycemia.

Alcohol [15]

Alcohol inhibits hepatic gluconeogenesis and therefore increases the risk of nocturnal hypoglycemia. Strategies to avoid hypoglycemia after alcohol intake include limiting alcohol intake to one serving for females and two servings for males, eating carbohydrate while drinking alcohol, using a temporary basal rate overnight, and eating carbohydrate before bed.

Travel [15]

When planning a trip, the first thing to consider is if the best option is to go to that particular trip using the insulin pump. If the trip is to the beach and the patient will be in contact with the sand and swimming a lot, the patient may decide to disconnect from the pump for those days. If deciding to do so, please review the next section.

When traveling with the pump, it is important to be prepared. One should instruct the patient to: Adapted from [15]–Chap. 4.
- Ensure you have all your supplies: Not just pump supplies and insulin but blood glucose and ketone monitoring, rapid-acting glucose supplies, glucagon kit, back-up syringes. and long-acting insulin.
- Keep supplies in a bag that stays with you at all times (cabin baggage). Extra pump reservoirs, infusion sets, and batteries can be kept in check-in luggage. If possible, give a smaller backup supply to someone travelling with you in case luggage is misplaced.
- For long-distance travel or travel in hot countries, keep insulin in an insulation bag, such as an evaporative cooling case.
- Ensure you keep documentation from your doctor confirming you have T1D and need to carry supplies with you and need to wear your pump at all times—this may be needed for airport security.
- Know where to obtain medical help if needed and keep key contact numbers.
- Locating and obtaining pump supplies can be a problem in some countries.
- Medical travel insurance is advised and ensures it covers your diabetes and pump use.
- If travelling in a group, make sure group members are aware that you have diabetes and what they may need to do in an emergency.
- Keep any reminders you may need, such as your pump settings, sick-day rules, and multiple dose injection doses.
- Change the time in the insulin pump and in the blood glucose meter when arriving to the destination.

Insulin Adjustments When Travelling

When traveling through time zones, the circadian rhythm will take time to adjust, and therefore, there can be an increased risk of hypo- or hyperglycemia. For this reason, while waiting for the body to adjust, it might be wise to set a flat basal rate at a slightly lower level (10–20% lower) than the usual basal rate for 24 h and return to the usual basal rate, once the body has adjusted.

In addition, if the trip will entail a lot of walking, temporary basal rates may be needed or setting a pattern for travel with lower rates. At the beginning, it will be important to have frequent BG measurements (every 3 h).

Insulin Pump Therapy on Vacation [15]

On occasions, people with T1D may want to rest from the insulin pump. This can be done when taking a beach vacation, as explained above, or when it is psychologically needed, but it can also occur as an unplanned situation because of pump malfunction. It is important that every patient that is on the pump knows how to go off and back on the pump.

Going Off the Pump

The first thing that needs to be done is to calculate the basal insulin dose that will be required.

In general, it may be safer to switch the total basal CSII dose to the basal insulin analogue dose on a 1:1 ratio and then make adjustments as needed [18].

If changing from the pump to glargine U100, the patient may require the same or an increase of up to 20% of the total basal insulin dose. This may be given in one or two doses.

If changing from the pump to degludec insulin, the patient may require the same amount of basal insulin, or a 5–10% increase. And this is usually given once a day.

It is important to note that the pump should be discontinued 2 h after the first long-acting insulin injection is given. If possible, it is best to do this in the morning to minimize the risk of problems at night.

The patient will need to check the BG and give himself the bolus insulin using his ICR and ISF, as usual. He can use the insulin pump as a bolus calculator, or learn how to do the calculations manually. If a bolus calculator app is available in the specific country, then he can use it with the pump settings.

Going Back on the Pump

When resuming pump treatment, the patient should usually return to his previous pump settings, unless significant changes in insulin dose have occurred. The best time to restart the pump is just before the long-acting insulin has worn off (approximately 2 h prior to the next due dose of long-acting insulin). If possible, it is advisable to do this in the morning. It is important to note that with the new ultra-long-acting insulins (degludec), it may be needed to use a lower temporary basal rate, until all of the ultra-long-acting insulin has been absorbed and metabolized (it may take up to five half-lives, though usually this is only necessary for the first 24 h).

CGM

There are three main ways in which once can monitor glucose levels:

- Blood glucose meters: These measure capillary BG levels at a specific time. The glucose meters that are on the market use an enzymatic method to measure BG levels, and it can be either hexokinase or glucose oxidase. There are several BG meters on the market. The patient should ideally measure before each meal, 2 h after each meal, before bedtime, and occasionally at 3:00 in the morning.
- Continuous glucose monitors: These continuously (approximately every 5 min) measure interstitial glucose levels. These depend on a sensor (also uses an enzymatic method that is converted to electrons), a transmitter, and a reading device. The ones that are coupled to insulin pump therapy display the CGM graph on the pump. Some glucose monitors can also have their information displayed on a smart phone. There are two main brands in the Market: Dexcom and Medtronic. So far, both need to be calibrated, twice a day, on steady-state conditions, with BG reading obtained via a BG meter. Both show a CGM glucose graph and arrows showing the glucose rate of change.
- Flash glucose monitor (Free Style Libre, Abbott): This system measures interstitial glucose levels every minute. It consists of a sensor and a reading device. The sensor is factory calibrated and uses also an enzymatic method (glucose oxidase), to continuously measure the interstitial glucose levels. It can store up to 8 h of information, if not scanned by the reading device. When scanned, it displays the glucose reading at that time, a graph of the glucose values in the last 8 h, and an arrow, showing the glucose rate of change.

Integrated Systems

To close the loop is the holy grail of the integrated systems for insulin delivery for the treatment of T1D. Many years ago, this was tried with the biostator and the back-pack insulin pump. But these technologies measured intravenous glucose and gave intravenous insulin infusions. Since these were complicated and large in size, they never made it into the market. Medtronic has been a pioneer in integrated systems for insulin delivery that have reached the market. The first system started using a CGM that was able to communicate with the pump and give an alarm in case of hypoglycemia. The second system, also called a sensor augmented pump, had the CGM communicate with the pump and stop the infusion at a target low glucose reading, this feature is called “low glucose suspend”-LGS. This feature has shown to reduce the time spent in hypoglycemia [19]. The third system that reached the market is the PREDICTIVE control, in which the insulin infusion is stopped when it predicts a hypoglycemic event in the next 30 min. It also restarts when

the glucose levels stabilize [20] (Medtronic 640G). In 2016, the FDA approved the first hybrid close loop system (Medtronic 670G) that has an algorithm for the basal rate and corrects for hyper- or hypoglycemia automatically. The patient still has to check his BG levels and count carbohydrates, in order to give a meal bolus or a correction bolus. In the 3-month study for its approval, no patient had severe hypoglycemia, nor DKA.

Medtronic's 780G® advanced hybrid closed loop system, which is now available in the United States, Europe, and some Latin American countries, also has a basal algorithm that allows to choose the goal at 100 mg/dL, 110 mg/dL, or 120 mg/dL and has the autocorrect function. This system uses the artificial pancreas algorithm developed by DreaMed Diabetes based on Physicians' Fuzzy Logic (Fuzzy Logic, MD), co-authored by Drs. Thomas Dane, Tadej Battelino, and Moshe Phillip [21].

There are currently a number of companies that are developing closed-loop systems. Most using the highly accurate Dexcom G6® Continuous Glucose Monitor. Examples are the Tandem T-Slim® pump with Control IQ® (Tandem Inc., USA), the CAM-APS FX [22] (Cambridge, UK), which works with an App on Android phones, and is only under development in Europe, the Omnipod Horizon®, which is a disposable micro-pump without a tube, and Diabeloop®. The results of pivotal studies in children and adults with the Omnipod Horizon System, which can lead to goals of 110–150 mg/dL, in 10 mg/dL increments, were recently published. Most adults achieved excellent overnight glucose control, with time in range > 70% in adults and 65% in children [23]. All of these systems still require the user to announce the food to calculate the meal bolus.

Several groups are working in the development of the close loop system. One particularly interesting is the one by the group of Damiano and Russell, from Boston University, Massachusetts General Hospital, Harvard Medical School. They are developing a bi-hormonal (insulin and glucagon) close loop system with great promise [24–28].

Since many patients are not waiting for the institutional regulatory approvals, some (mostly engineers and technology savvy) have created their home made CGM-insulin pump integrated systems, with great success, increasing their time in blood glucose target range [29, 30].

Conclusions

Insulin pump therapy is an excellent tool to improve glycemic control and quality of life. To obtain the full potential of this therapy, an experienced multidisciplinary team approach should be established. It must be stressed out that continuous close professional advice should be available, especially at the beginning in order to make the adequate adjustments as soon as possible. It may take up to a month or more to adjust all the settings. In addition, when having significant life changes (childhood, puberty, pregnancy, menopause, aging, travelling, exercise), adjustments will need to be made in the therapy.

There have been significant advances in insulin pump therapy technology in recent years. This chapter focuses mostly in starting insulin pump therapy using capillary BG measurements for the initial adjustments and does not deepen into the use of integrated systems. Although CGM technology can help significantly in doing adjustments and reducing hypoglycemia, these technologies are not available in all the countries. Therefore, it is beyond the scope of this chapter to train in how to take full advantage of CGM technology and integrated systems. If a healthcare professional is interested in further deepening his knowledge, he should reach out to the insulin pump providers in their country.

Suggested Additional Reading

Medtronic Protocol—(4).

AACE 2014—(1).

INSULIN PUMPS AND CGM MADE EASY—(16).

Wolpert H, Smart Pumping—(5).

Peters AL, Endocrine Society Guidelines 2016 (3).

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Multiple Choice Questions

1. What type of insulin can be used on an insulin pump?
   (a) **rapid human insulin and fast acting insulin analogues**
   (b) basal insulin analogues
   (c) NPH insulin
   (d) basal- and fast-acting insulin analogues
2. How is the total daily insulin dose calculated?
   (a) Weight in kg × 0.5
   (b) Previous total daily dose × 0.75
   (c) Taking the average of a and b
   (d) **All of the** above **are correct**
3. How is the basal rate calculated?
   (a) Total daily dose × 0.5, divided by 24 h
   (b) Weight in kg × 0.5
   (c) C. Total daily dose divided by 24 h
   (d) D. 2000/total daily dose
4. How is the food insulin bolus calculated?
   (a) **By the insulin to carbohydrate ratio**
   (b) By the insulin sensitivity factor

(c) By the basal rate
(d) Using temporary basal rates

5. What is the formula to calculate the insulin to carbohydrate ratio?
   (a) **450/total daily dose**
   (b) 2000/total daily dose
   (c) Weight in kg × 0.5
   (d) Weight in kg × 0.8
6. How is the correction bolus calculated?
   (a) By the insulin-to-carbohydrate ratio
   (b) **By the insulin sensitivity factor**
   (c) By the basal rate
   (d) Using temporary basal rates
7. What is the formula to calculate insulin sensitivity factor?
   (a) 450/total daily dose
   (b) **2000/total daily dose**
   (c) Weight in kg × 0.5
   (d) Weight in kg × 0.8
8. What kind of delivery bolus options exist?
   (a) **Normal, dual, and square**
   (b) Manual and dual
   (c) Normal and temporary
   (d) Manual, dual, square, and temporary
9. What does the patient need to do in case of having two blood glucose values above 240 mg/dL despite correction?
   (a) **Measure ketones; look for a possible cause (i.e., cannula occlusion or dislodgement); correct with an insulin injection (with insulin syringe or pen); change the insulin, insulin reservoir and infusion set**
   (b) Give a correction bolus
   (c) Wait for insulin to act
   (d) Set an increase in temporary basal rate
10. Do the math for initial basal rate, insulin-to-carb ratio and insulin sensitivity factor: Forty-year-old, female patient, A1c 7%, weight 60 kg, actual insulin regimen 22 IU glargine and 8 IU lispro before each meal (3 meals).
    (a) Basal rate: 0.625 IU/h; ICR: 15 g; ISF: 70 mg/dL (calculated by weight)
    (b) Basal rate: 0.700 IU/h; ICR: 13 g; ISF: 60 mg/dL (calculated by previous dose)
    (c) Basal rate: 0.650 IU/h; ICR: 14 g; ISF: 60 mg/dL (average of a and b)
    (d) **All are valid options to consider to start, if risk of hypoglycemia is a particular concern, start with option a**

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Part VII

Cardiovascular Risk Factors

Diabetes and Hypertension

39

Hasan Syed, Sowjanya Naha, Dharshan Khangura, Michael Gardner, L. Romayne Kurukulasuriya, and James R. Sowers

Objectives

- To explore the contemporary understanding of the pathophysiology of HTN complicating diabetes
- To review large scale clinical trials assessing HTN treatment goals and outcomes in diabetes
- Identify the indications for ambulatory BP monitoring
- Interpret HTN guidelines from different organizations
- To review glycemic lowering drugs that can reduce BP

Introduction

According to the United States (US) Centers for Disease Control and Prevention 2020 National Diabetes Statistics Report, 68.4% of patients over the age of 18 diagnosed with diabetes mellitus (DM) also have hypertension (HTN). A total of 34.2 million people or 10.5% of the US population has diabetes. DM has been diagnosed in 8.2% or 26.9 million. This is an underestimate due to under diagnosis of DM. Therefore, 7.3 million people or 21.4% were undiagnosed. Thus, a significant portion of the population has both DM and HTN, which predisposes them to

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cardiovascular disease (CVD) and chronic kidney disease (CKD) [1]. In patients with DM and HTN, CVD is the key cause of premature morbidity and mortality and is the greatest contributor to health care costs. Therefore, the importance of screening for HTN is paramount and should be done at every routine office visit [2]. Indeed, the 2020 Canadian HTN guidelines also recommend that newly diagnosed patients with HTN be screened for diabetes using a fasting glucose and/or hemoglobin A1c. They also consider recommending an intensive systolic blood pressure (BP) target of <120 in appropriate patients with CKD. In the Centers for Disease Control and Prevention National Diabetes Statistics Report, HTN was defined as BP greater than or equal to 140/90 mmHg or taking prescription medications for treatment of HTN [3]. Independent of other CVD risk factors, HTN shows a significant increase in CVD that is incremental with each 20 mmHg rise of systolic BP and 10 mmHg rise of diastolic BP across the range from 115/75 to 185/115 mmHg. Patients with DM typically have additional risk factors apart from DM itself such as dyslipidemia, obesity, physical inactivity, vascular stiffness, and microalbuminuria, which further elevate CVD and CKD risk [4].

Pathophysiology

The pathophysiology of HTN in DM is multifactorial, involving multiple organ systems, metabolic signaling pathways, and environmental and genetic factors. Adipose tissue, when located disproportionately in the abdomen (visceral adiposity), is associated with insulin resistance, HTN, hyperglycemia, and a pro-inflammatory state [4]. Bioactive molecules and hormones referred to as adipokines have altered secretion in obesity, which contributes to obesity-related insulin resistance and HTN. Angiotensinogen, aldosterone-stimulating factor, dipeptidyl peptidase, leptin, adiponectin, resistin, tumor necrosis factor (TNF), interleukin 6, and complement-C1q TNF-related protein 1 (CTRP1) are examples of such pro-inflammatory adipokines that are increased with increased visceral adiposity [5, 6].

Insulin resistance is strongly associated with endothelial dysfunction, which results in impaired vascular relaxation and arterial stiffness, which is a biomarker for increased CVD. Impaired insulin metabolic signaling in insulin-resistant states such as obesity and type 2 DM is characterized by impaired serine phosphorylation of insulin receptor substrate-1 (IRS-1) and downstream phosphionositide 3-kinase, protein kinase B activation leading to reduced endothelial nitric oxide (NO) synthase activation and NO bioavailability in the vasculature. In insulin resistance, there is impairment of insulin growth factor signaling with activation of extracellular signal-regulated kinase (ERK1/2) and upregulation of endothelin-1, which contributes to increased vascular contraction and maladaptive growth and remodeling [5, 6].

The systemic and tissue renin-angiotensin-aldosterone system (RAAS) is often inappropriately activated in insulin-resistant states. In part, this is related to increased angiotensin II (Ang II) and aldosterone production by omental adipose tissue. Ang II and aldosterone may also inhibit insulin metabolic signaling in endothelial cells and vascular smooth muscle cells, as well as classical insulin sensitive tissues such as skeletal muscle, adipose, and liver tissue. There is increasing evidence that the inappropriate activation of RAAS is a major contributor to progression of CVD and chronic kidney disease (CKD) as it relates to endothelial dysfunction and arterial stiffness in insulin-resistant states [7].

Angiotensinogen and Ang II are produced in increased amounts in adipose tissue under oxidative stress and chronic low-grade inflammation. CTRP1 in rodent models of obesity and insulin resistance promotes the production of aldosterone [5]. Ang II and aldosterone activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a major source of reactive oxygen species, which promotes oxidative stress and impaired NO-mediated vasodilation. Furthermore, aldosterone has been shown to increase epithelial sodium channel (eNaC) expression on the endothelial cell surface, thereby promoting endothelial cell cytoskeleton cortical stiffness. Increased uric acid, as a result of consumption of diets rich in fructose, also appears to contribute to immune and inflammatory responses leading to RAAS activation, endothelial dysfunction, and increased vascular stiffness [5, 7].

At the level of the nephron, the sodium-glucose cotransporter-2 (SGLT2) is a low-affinity, high-capacity transporter that is primarily responsible for plasma glucose reabsorption in the proximal convoluted tubule. In DM, glucose reabsorption is increased due to increased expression of SGLT2 associated with glomerular hyperfiltration causing glucose toxicity along with sodium reabsorption and retention [6]. Hyperinsulinemia may also cause sodium retention via increased expression of sodium transporters like eNaC in the distal nephron and increased activation of the sodium hydrogen exchanger in the proximal tubule (Fig. 39.1) [5].

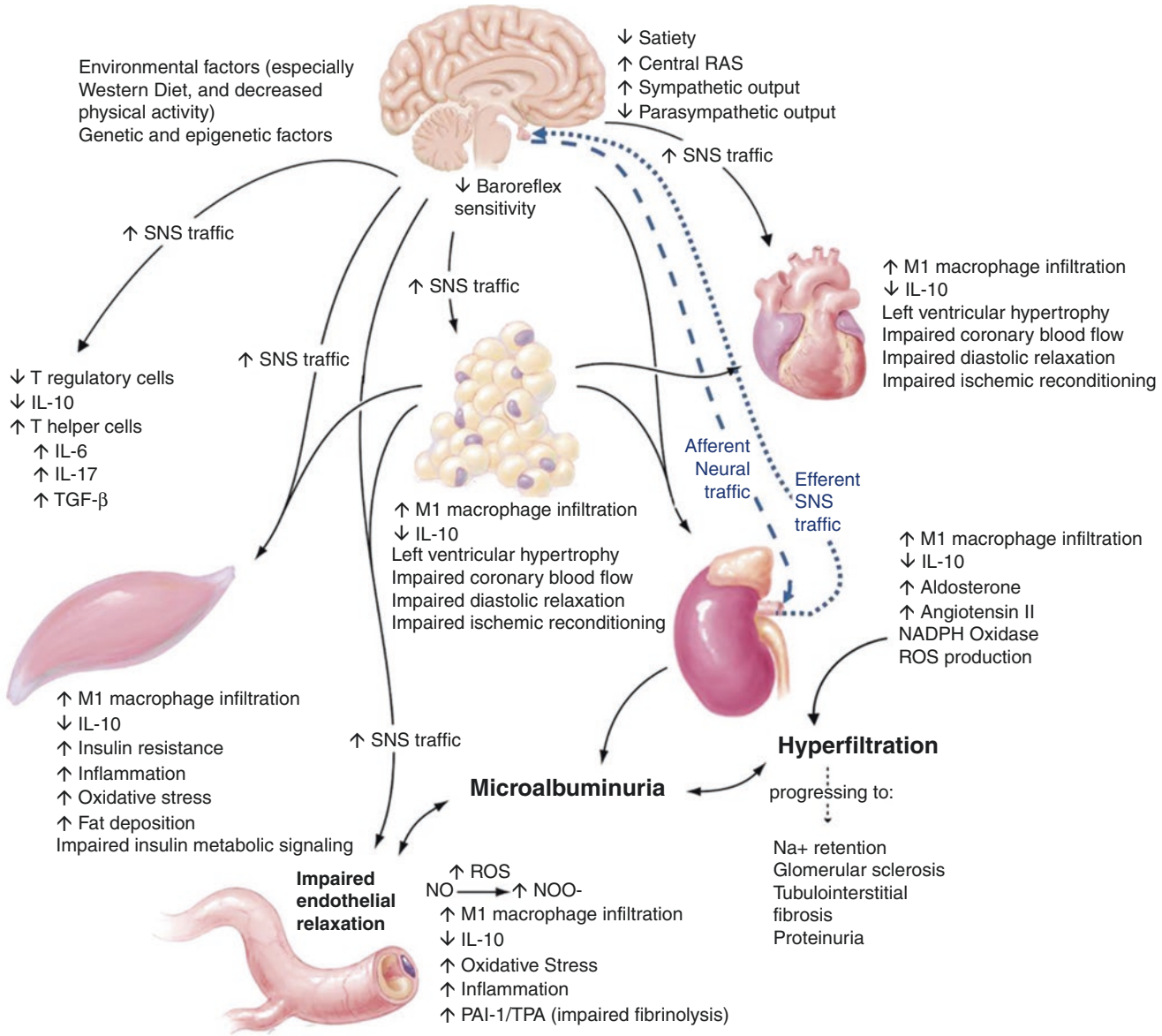

Fig. 39.1 Systemic and metabolic factors that promote coexistent diabetes mellitus, hypertension, cardiovascular, and chronic kidney disease. (Used with permission from Sowers JR. Recent advances in hypertension. J Am Heart Assoc. 2013;61:943–947)

Large-Scale Trials Assessing HTN

- United Kingdom Prospective Diabetes Study (UKPDS)
- Hypertension Optimal Treatment (HOT)
- The Action in Diabetes and Vascular disease, PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE)
- Appropriate Blood Pressure Control in Diabetes (ABCD)
- Systolic Hypertension in Europe (Syst-Eur)
- The Action to Control Cardiovascular Risk in Diabetes (ACCORD)
- The International Verapamil SR—Trandolapril (INVEST)
- The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)
- Veterans Affairs Diabetes Trial (VADT)
- Systolic Hypertension in the Elderly Program (SHEP)
- Systolic Blood Pressure Intervention Trial (SPRINT)

Review of the Evidence

Evidence of the management of HTN in diabetic patients was sparse prior to the Hypertension in Diabetes Study (HDS) in 1998. Since then, there have been many large-scale trials that have examined BP control and CVD outcomes. The United Kingdom Prospective Diabetes Study (UKPDS) aimed to study the intensity of BP control and its effect on clinical outcomes in a subset of the group. Comparisons

were made of intensive control with a goal of <150/85 mmHg versus less intensive control with a goal of <180/105 mmHg. The median follow-up was 8.4 years, and mean BP in the intensive group was 144/82 mmHg compared to 154/87 mmHg in the less intensive group. A significant reduction in diabetes-related death, stroke, heart failure, and microvascular disease such as retinopathy was seen in the intensive group [8]. The ADVANCE study showed that reducing systolic BP by 5.6 mmHg and diastolic BP by 2.2 mmHg compared to placebo conferred a risk reduction of 8% for macrovascular events, 9% for microvascular events, and 18% for CVD death. The intervention in this study was adding a fixed dose perindopril/indapamide to existing standard therapy. The ABCD study treated DM patients with HTN and high normal BP with goal systolic BP of <130 mmHg. The HTN group's mean BP was 132 mmHg, and the high normal group achieved a mean BP of 128 mmHg. The HTN group had reduced total mortality, and the high normal group had reduced incidence of stroke and decreased progression of nephropathy. The Syst-Eur study showed a decrease in overall mortality and morbidity related to CVD events in diabetic and nondiabetic populations by lowering systolic BP [9].

The ACCORD study compared intensive BP control (<120 mmHg systolic) versus standard BP control (<140 mmHg systolic) and found no statistically significant difference in CVD but did see a reduction in stroke in the intensive group. However, the intensive group was associated with increased risk of hypotension, bradycardia, hyperkalemia, and renal impairment [10]. After observational analysis, the INVEST study showed that the group with goal systolic BP <130 mmHg compared to goal 130–139 mmHg had marginally increased all-cause mortality, and the group with systolic BP of <110 mmHg had significant increase in all-cause mortality (hazard ratio 2.18) [11]. The ONTARGET study examined CVD risk reduction with particular attention to baseline BP. They found significant reduction in CVD with a baseline systolic BP >140 mmHg [12], less reduction if baseline was <130 mmHg, but continued benefit for stroke reduction with lower baseline BP. The VADT study along with the ONTARGET study showed an increased risk of myocardial infarction and CVD events with low diastolic BP. In the VADT study group, diastolic BP was <70 mmHg with a systolic BP 130–139 mmHg [13]. The SPRINT trial aimed for a target systolic BP of 120 mmHg in adults 50 years of age or older with HTN and saw a significant reduction in CVD. This trial showed an associated 33% reduction of heart attack, heart failure, and stroke and a 25% reduction of death compared to a target systolic BP of 140 mmHg. Diabetic patients and patients with a history of previous stroke were excluded from this trial [14].

Guidelines and BP Targets

The most recent National Committee on Prevention, Detection, Evaluation, and Treatment of High BP (JNC 8) was released in 2014. They based their recommendations on evidence from randomized control trials (RCT), expert opinion, and the quality of evidence, which differed from the JNC 7 panel that included observational trials. JNC 8 recommends initiating pharmacological therapy to lower BP to a goal of <140/90 mmHg in patients age > 18 with DM. The ACCORD-BP study supported this lower systolic BP goal of <140 mmHg in the diabetic population compared to <150 mmHg in the nondiabetic population. Major trials such as Syst-Eur, UKPDS, and SHEP studies supported the conclusion that treatment to a systolic BP of <150 mmHg lowers mortality and improves CVD and cerebrovascular health outcomes. The HOT trial found that a diastolic BP reduced to <80 mmHg was associated with a reduction in major cardiovascular events when compared to <90 mmHg and < 85 mmHg by 51% and 24%, respectively. However, JNC 8 determined that this study was not of sufficient quality to recommend a lower diastolic goal, as it was a post hoc analysis of a small subgroup of the study population [9].

The European Society of Cardiology and European Association for the Study of Diabetes recommends systolic BP(SBP) of 130 or below for diabetics treated for hypertension if tolerated. In patients 65 or older, the SBP target range of 130–140 mmHg is recommended if tolerated. In all patients with DM, SBP should not be lowered to <120 mmHg. Diastolic blood pressure (DBP) should be lowered to <80 mmHg but not <70 mmHg. If office SBP is ≥140 mmHg and/or DBP is ≥90 mmHg, drug therapy is recommended in combination with non-pharmacological therapy [15].

The European Society of Hypertension and European Society of Cardiology as part of their 2018 guidelines recommend that antihypertensives should be started in diabetics, when office BP is ≥140/80 mmHg, aiming at an SBP of 130 mmHg. If treatment is well tolerated, treated SBP values of <130 mmHg should be considered because of the benefits on stroke prevention. SBP values of <120 mmHg should be avoided. In patients over 65 years of age, treating to a target SBP range of 130–139 mmHg is recommended. They recommend targeting DBP < 80 mmHg, but not <70 mmHg. In diabetic or nondiabetic patients with CKD, it is recommended to lower SBP to a range of 130–139 mmHg [16].

The International Society of Hypertension Global Hypertension Practice Guidelines recommend that blood pressure should be lowered if BP is ≥140/90 mmHg and treated to a target of <130/80 mmHg (< 140/80 in elderly patients) in diabetics [17].

The American Diabetes Association (ADA 2021 guidelines) recommends a BP goal of less than 130/80 for indi-

viduals with diabetes and hypertension at higher cardiovascular risk (existing atherosclerotic cardiovascular disease [ASCVD] or 10-year ASCVD risk ≥15%) if it can be safely attained. In diabetics with hypertension at lower risk for cardiovascular disease (10-year atherosclerotic cardiovascular disease risk <15%), ADA guidelines recommend a blood pressure target of <140/90 mmHg. In pregnant patients with diabetes and preexisting hypertension, a blood pressure target of 110–135/85 mmHg is suggested to reduce the risk for accelerated maternal hypertension and minimizing impaired fetal growth [2]. The American Association of Clinical Endocrinology (AACE) and American College of Endocrinology (ACE), in their 2015 clinical practice guidelines, recommend a goal of approximately 130/80 mmHg in pre-DM and DM patients with HTN. They also indicate that the goal should be individualized based on patient age, duration of disease, and comorbidities. If patients have complex comorbidities, are frail, or experience adverse effects of medications, a more relaxed goal is supported. If this can be achieved safely without adverse medication effects, a more intensive goal of 120/80 can be used [18].

The appropriate target goal for BP In the diabetic population has been the subject of much debate, as control is related to reduction in CVD and kidney disease. There have been many large-scale trials with discrepant results, which have led to confusion. The JNC 7 advocated a target of 130/80 mmHg; however, the trials that used these parameters rarely achieved the target systolic BP and were limited to only a few studies. Consideration of more recent trials such as SPRINT, post hoc analysis of ACCORD, and meta-analysis suggest that a more aggressive systolic BP target of <130 mmHg may be more appropriate than the systolic target of 140 mmHg that was recommended by JNC 8. Wu et al. analyzed a large Chinese cohort of 101,510 individuals with data from 2006 to 2014. The study involved patients with established DM and excluded those who had a BP >140/90 mmHg, were taking antihypertensives, were previously diagnosed with HTN, or had baseline CVD or cancer, in an effort to reduce confounding of mortality outcomes. This left them with 2311 diabetic, normotensive patients whom they examined whether BP of <120/80 mmHg had increased mortality. Their data suggested an increase in CVD events in patients with BP <120/80 mmHg [19]. It is important to note that in this study the participants were predominantly male and had early-stage DM without complications, whereas the ACCORD and SPRINT trials included high-risk hypertensive patients treated to a goal. Based on the collective data from all of the above trials, it appears that there may be a sweet spot to target between 120 and 135 mmHg systolic BP and that a more aggressive target of <120/80 mmHg may be considered for select diabetic patients at the highest risk for stroke [20]. An individual patient tolerance of medications and comorbidities must be considered when managing HTN.

Lifestyle Modification

Approach to weight loss and maintenance based on National Institutes of Health (NIH) clinical guidelines for treatment of obesity [21, 22]:

- Low calorie diet (800–1200 kcal/day): 8% weight loss over 6 months, reduces abdominal fat.
- Very low calorie diet (250–800 kcal/day): similar long-term weight loss, greater initial weight loss compared to low calorie diet.
- Aerobic exercises: Modest weight loss, improve cardiorespiratory fitness, may reduce abdominal fat.
- Physical activity + reduced caloric intake: greater weight loss than either alone.
- Add behavioral therapy to weight loss approach: additional short-term benefits.
- Initial weight loss goal: 10% reduction from baseline weight.
- Target weight loss: 1–2 pounds/week for 6 months.
- Start with moderate physical activity: 30–45 min at least 3–5 days/week.
- Bariatric surgery: BMI > 40 kg/m^2 or > 35 kg/m^2 with high-risk obesity-related morbidity and failed less invasive measures.

The most important therapy whether initial or in combination with pharmacotherapy is lifestyle modification. This involves reduced dietary sodium intake (<2 g/day), weight loss, physical activity, and moderation of alcohol intake. Moderation of alcohol intake is defined as less than two drinks or less in a day for men and one drink or less for women [23]. In the United States, one standard drink contains roughly 14 g of pure alcohol, which is found in 12 oz. of regular beer, 5 oz. of wine, 8–9 oz. of malt liquor, and 1.5 oz. of distilled spirits such as vodka, rum, gin, tequila, and whiskey [24]. In the NIH-funded Look AHEAD (Action for Health in Diabetes) trial, the impact of intensive lifestyle modification (ILI) including diet, physical activity, and behavioral modification on adults with DM type 2 was evaluated [25]. They compared their intervention to that of usual care of DM using diabetes support and education. At 1 year, the ILI group lost 8.6% of their initial body weight compared to 0.7%, decreased mean hemoglobin A1c −0.64 compared to −0.14, decreased systolic BP –6.8 mmHg compared to −2.8 mmHg and had a larger decrease in metabolic syndrome 93.6–78.9% compared to 94.4–87.3%, all of which were statistically significant [26].

Evidence demonstrates that excess dietary consumption of sodium impacts not only one's BP but also several other BP-independent effects. Sodium can affect multiple organ systems in the body, including neurologic, cardiac, renal, and vascular. It has been shown that high sodium intake is also

associated with increased glucocorticoid production, insulin resistance, and metabolic syndrome [27]. In many countries, public health recommendations include sodium restriction to less than 5–6 g per day. However, the Cochrane systemic review and multi-study meta-analysis demonstrated that a further reduction in sodium will lower BP even further [28]. The Dash-Sodium study, a multicenter, 14-week randomized feeding trial, followed three different dietary intakes of sodium for 1 month: (3.3 g, 2.4 g, and 1.5 g). The greatest BP drop was noticeable within the group with the greatest sodium restriction [29]. The US Department of Agriculture and Department of Health and Human Services currently recommend consumption of 2.3 g or less of sodium per day in adults.

In addition to sodium restriction, diet modification can have a positive impact on not only BP but also in the treatment of obesity. Two specific diets that have shown to be particularly effective are the Dietary Approaches to Stop HTN (DASH) diet and the Mediterranean diet. The DASH diet is based on the premise of a diet high in whole grains, fish, poultry, fruits, vegetables, low-fat dairy products, and reduced saturated and total fats. In essence, the diet is rich in potassium, magnesium, calcium, protein, and fiber. In the original DASH studies, carbohydrates supplied 55% of calories, total fats 27% of calories, proteins 18%, and saturated fats 6% [30]. The diet should consist of at least six to eight daily servings of grains, less than six servings of lean meats (poultry and fish), four to five daily servings of fruits and vegetables, two to three servings of low-fat milk products and fats and oils, and five or less servings per week of sweets, nuts, seeds, and legumes [31].

The first DASH feeding trials resulted in participants having lower BP and LDL cholesterol endpoints with statistical significance. Systolic BP was reduced on average by 11.4 mmHg ($P < 0.001$), and diastolic BP was reduced on average by 5.5 mmHg ($P < 0.001$). Seventy percent of participants had normal BP (goal SBP <140 and DBP <90 mmHg) at the end of the trial compared to 23% on the control diet [32]. Compared to controls, the DASH diet also reduced the estimated 10-year CVD risk by 18%. The relative risk ratio compared to controls at 8 weeks with baseline 10-year CVD risk was 0.82 (95% CI, 0.75–0.90, $P < 0.001$). In other studies, the DASH diet also decreased pulse wave velocity (PWV) over time ($p = 0.014$) reaching significance after 2 weeks ($p = 0.026$) [33]. Additional information on PWV will be provided later in this chapter.

The Mediterranean diet embodies the Mediterranean culture and lifestyle. Although there are now many variants of this diet, the traditional premise comprises low amounts of saturated fats, meat and meat products, and consumption of high amounts of olive oil, fruits, vegetables, cereals, legumes, nuts, moderate amounts of fish and dairy products, and wine in moderation [34]. Unlike the DASH diet, the Mediterranean diet has an increased consumption of the total amount of fats, up to 40% of caloric intake, with less than 7–8% of caloric intake consisting of saturated fats [35]. In the Greek European Prospective Investigation into Cancer and Nutrition (EPIC) prospective cohort study, lower consumption of meat and meat products, higher consumption of vegetables and fruits, and minimization of saturated fats with more monounsaturated fats were considered most beneficial with a higher predictive score of lower mortality [36]. In addition to diet, regular physical activity and culture-specific psychosocial support played an integral part in the Mediterranean diet. Meals were often consumed with others with frequent rest after meals that presumably reduced overall stress. In addition, mealtime interactions can also be correlated with dietary adherence (Fig. 39.2) [37].

The Mediterranean diet is associated with reduced all-cause mortality and reduced cardiovascular mortality in addition to improved health. A systematic review of 2824 studies with eight meta-analyses and five randomized controlled trials (RCTs) was done in 2015 that compared the Mediterranean diet to a control diet in patients with DM2 and prediabetic states. These studies demonstrated remission of metabolic syndrome, favorable effects on body weight, total and LDL cholesterol, and overall reduced risk of future diabetes by 19–23% [38]. The Prevencion con Dieta Mediterranea trial (PREDIMED) was a parallel-group, multicenter, randomized trial that studied primary cardiovascular prevention when comparing Mediterranean diets to a low-fat control diet. Although there was not a noted effect on all-cause mortality, results were suggestive of a protective effect with noted unadjusted hazard ratios of 0.7 ($p = 0.015$) when compared to the control diet. There was an absolute risk reduction in approximately three major cardiovascular events per 1000 person-years [39].

Combining the Mediterranean diet with a healthy lifestyle, avoidance of tobacco products and regular exercise has shown to have a positive outcome with reduced mortality rate. The Healthy Ageing Longitudinal study in Europe (HALE) project was conducted between 1988 and 2000 that showed a 50% lower rate of all-cause and cause-specific mortality in individuals aged 70–90 years of age who adhered to the Mediterranean diet with a heathy lifestyle [40]. In the exercise and nutrition intervention for cardiovascular health (ENCORE) study, combining the DASH diet with weight management resulted in larger BP reductions with improved secondary outcomes in vascular and autonomic function and reduced left ventricular mass. Up to 12.5 mmHg systolic and 5.9 mmHg diastolic reduction in BP was observed in the DASH diet combined with a behavioral weight management program [41].

Aerobic exercise is not only effective in weight loss but also thought to lower BP independent of weight loss [42]. According to the recommendations from American College

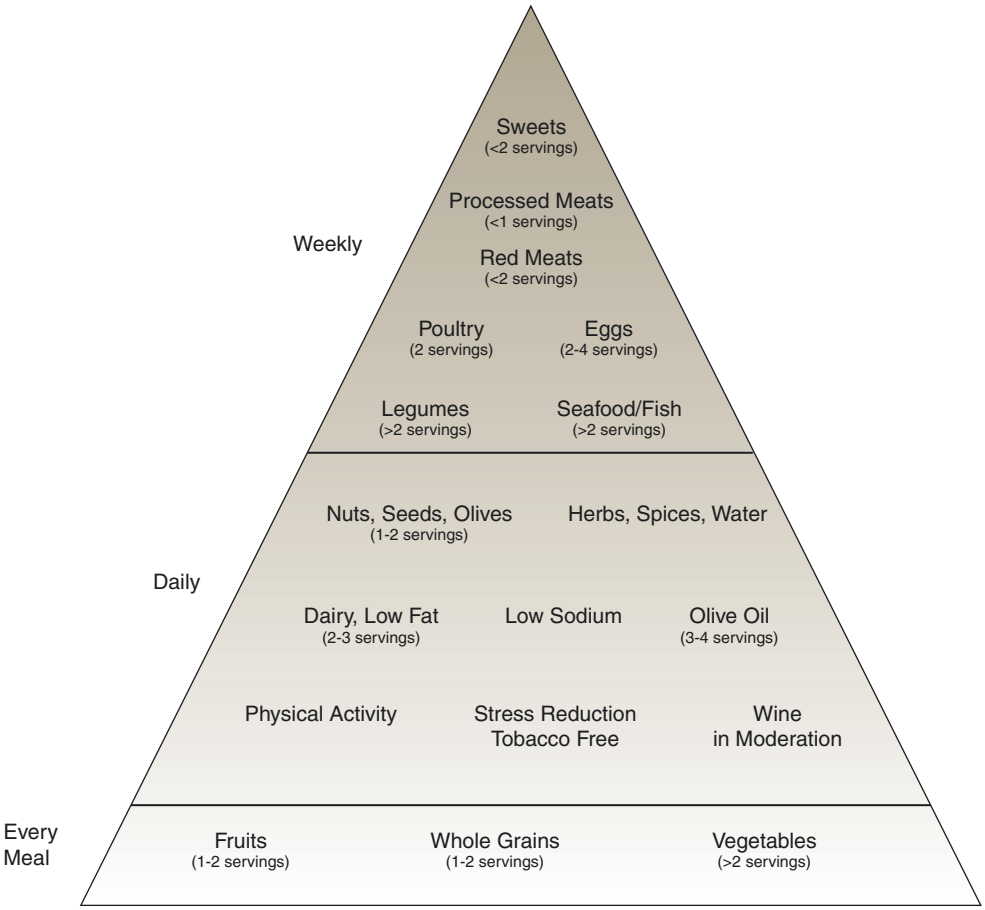

Fig. 39.2 Mediterranean diet pyramid

of Sports Medicine and American Heart Association, all healthy adults should engage in moderate-intensity aerobic physical exercise for minimum of 30 min for 5 days per week, vigorous-intensity activity minimum of 20 min for 3 days per week or combination of moderate, and vigorous-intensity activity [43]. Moderate-intensity physical activity should target a heart rate of 50–70% of his or her maximum heart rate (MHR). The MHR (calculated as 220 minus your age) is the upper limit of what your cardiovascular system can handle during exercise. For example, a 40-year-old patient should sustain heart rate between 90 and 126 for 30 min (0.5 or 0.7 × [220–40]). Vigorous-intensity physical activity should target 70–85% of his or her MHR. However, a 2011 review suggests that the MHR prediction in adults that are overweight or obese can be more accurately determined using a MHR equation: 208–0.7 × age [44]. Per the American College of Sports Medicine Position Stand, a minimum of 150 min of moderate-intensity activity per week with an energy deficit of 500–1000 kcal per day is recommended for continued weight loss. With a structured and supervised exercise program, weight loss can be maximized [45].

There are multiple ways in which lifestyle modification can be implemented; however, the common ingredient is significant determination and effort on the part of the patient with the support of a multidisciplinary team. Not only is it effective, as was evidenced by the Look AHEAD trial, but it could also reduce financial burden and adverse events as a result of fewer medications needed for treatment. At 9.6 years of follow-up, the ILI group used less insulin, antihypertensives, and statins compared to the control group [26].

DM Medications

The following are diabetes medications/classes shown to reduce BP:

- Thiazolidinedione
- Glucagon-like peptide-1 (GLP-1) receptor agonist
- Dipeptidyl diphosphatase 4 (DPP-4) inhibitor
- Sodium–glucose cotransport 2 (SGLT2) inhibitor
- Bromocriptine mesylate

GLP-1 receptor agonist exenatide had a significant effect on BP reduction [46]. When studied in 120 patients, after 52 weeks, there was a decrease in BP with a greater effect

observed when the baseline BP was higher. In patients with a baseline systolic BP >130 mmHg, there was a reduction of 11.4 mmHg in systolic BP and a reduction of 3.6 mmHg in diastolic BP. In patients with a mean BP of 128/78, there was a reduction of 6.2 mmHg in systolic BP and a reduction of 2.8 mmHg in diastolic BP. These reductions were independent of both weight loss and medication changes. Exenatide has the benefit of once weekly dosing and causes weight loss in a dose-dependent fashion. It has been shown to cause weight loss in 75% of patients at 30 weeks with average loss of 4 kg, and like its effect on BP, greater effect is seen with patients with a higher BMI (>30 kg/m^2) at baseline [47]. Exenatide is thought to have both natriuretic and vasodilator properties [48, 49]. In a case series of 12 patients who took exenatide over a 12-week period, noticeable increases in plasma concentrations of vasodilators, cyclic guanosine monophosphate (cGMP), cyclic adenosine monophosphate (cAMP), and atrial natriuretic peptide (ANP) while suppressing the RAAS suggest vasodilator and natriuretic properties [50]. Further evidence suggests that exenatide may also have diuretic and renal vasodilator effects. Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial demonstrated a sustained decrease in BP (SBP/DBP –1.2/−0.6 mmHg) with a slight increase in heart rate (3 bpm.) [51]. In a meta-analysis of 25 trials with once a week exenatide and daily liraglutide, it was shown that GLP-1 receptor agonists had beneficial effects on systolic and diastolic BP [52].

Insulin resistance intervention after strole (IRIS) III study showed that addition of 30 mg of pioglitazone for 20 weeks to the existing medication regimen of 2092 diabetics with A1c between 6.6% and 9.9% reduced systolic BP from 141 to 137 mmHg and diastolic BP from 83 to 81 mmHg. Interestingly, fewer or even no antihypertensives were needed in 25% of previously hypertension-treated patients at the end of the study [53]. Thiazolidinedione's mechanism of action is through activation of peroxisome proliferator-activated nuclear receptors (primarily PPARγ receptor) and subsequent upregulation of genes decreasing insulin resistance. Studies have shown that lowering the expression of PPARγ receptors increased BP [54]. Some evidence suggests vasodilatory effects through inhibition of arginine vasopressin and norepinephrine responses and direct vascular effect through inhibition of calcium uptake of vascular smooth muscle [55, 56].

The DPP4 inhibitors, in addition to hyperglycemic control, have been shown to have a modest effect on BP, as well as a favorable effect on atherosclerosis, stroke and CVD. Sitagliptin, a DPP4 inhibitor, was used in a small study and showed a statistically significant reduction of −2.0 mmHg to −2.2 mmHg in systolic BP and −1.6 mmHg to −1.8 mmHg in diastolic BP [57]. One proposed mechanism includes upregulation of GLP-1, increasing NO bioavailability and therefore improving overall endothelial function in HTN [58, 59].

SGLT2 inhibitors have been reported to be associated with weight loss and to act as osmotic diuretics, resulting in lowering of BP [60]. One meta-analysis indicated a significant reduction in systolic and diastolic BP with a weighted mean difference of −2.46 mmHg in SBP and weighted mean differences of −1.46 mmHg for DBP. The weighted mean difference for the effect of SGLT2 inhibitors on body weight was −1.88 kg across all studies. There were no heart rate changes [61]. Another metanalysis with clinical trials with a duration of at least 12 weeks comparing SGLT-2 inhibitors with placebo or active drugs showed that patients on SGLT-2 inhibitors had statistically significant −1.2 reduction in systolic BP and −1.9 reduction in diastolic BP [62]. Clar et al. reported that dapagliflozin treatment was associated with a reduction in SBP ranging from −1.3 to −7.2 mmHg in the patients treated with doses of 10 mg [63]. Rosenstock et al. reported a reduction in SBP in response to canagliflozin treatment ranging from −0.9 mmHg with 50 mg once daily to −4.9 mmHg with 300 mg once daily (compared to −1.3 mmHg with placebo and −0.8 mmHg with sitagliptin) [64]. Inhibitors of sodium-glucose co-transporter-2 reduce BP beyond the projected impact of weight reduction on BP. A large-scale multicenter RCT has demonstrated that treatment with an SGLT-2 inhibitor, empagloflozin, was associated with small reductions in systolic/diastolic BP, weight, waist circumference, and uric acid levels compared to placebo. Results also indicated reduced risk of death from CVD, nonfatal myocardial infarction, nonfatal stroke, and death from all causes [65].

Large randomized controlled trials have reported statistically significant reductions in cardiovascular events for three of the SGLT-2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) and four GLP-1 receptor agonists (liraglutide, dulaglutide, semaglutide, and albiglutide) [2]. We now have data from several trials that indicate CV benefits from the use of glucose-lowering drugs in patients with CVD or at very high/high CV risk. The results obtained from these trials strongly suggest using both GLP1-RAs (LEADER, SUSTAIN-6, Harmony Outcomes, REWIND, and PIONEER 6) and SGLT2 inhibitors (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and CREDENCE), in patients with T2DM with prevalent CVD or very high/high CV risk [15]. Meta-analyses of the trials reported to date suggest that in type 2 diabetes with established ASCVD, GLP-1 receptor agonists, and SGLT2 inhibitors reduce risk of atherosclerotic major adverse cardiovascular events to a comparable degree [66]. SGLT2 inhibitors also appear to reduce risk of heart failure hospitalization and progression of kidney disease in patients with established ASCVD, multiple risk factors for ASCVD, or diabetic kidney disease [67]. It is unknown whether the use of both classes of drugs will provide an additive cardiovascular outcomes benefit [2].

Bromocriptine Mesylate quick release (Cycloset) is a quick release dopamine receptor agonist indicated for treatment of type 2 diabetes. This is a micronized formulation. Proposed mechanism of actions is reestablishing morning brain dopamine D2 receptor activity, reducing sympathetic tone, and

increasing insulin sensitivity. These actions lead to improved post prandial hyperglycemia. Study with 15 poorly controlled diabetics on metformin and GLP-1 agonist showed that bromocriptine mesylate caused a significant reduction in blood pressure compared to placebo. Systolic (134 ± 4 vs. 126 ± 6 mmHg), diastolic (78 ± 3 vs. 73 ± 4 mmHg), and mean arterial blood pressure (97 ± 5 vs. 90 ± 4 mmHg) all decreased significantly ($P < 0.05$) [68]. Some patients may end up with orthostatic hypotension. Another study with 1791 patient on metformin addition of bromocriptine Mesylate has shown to reduce cardiovascular risk compared to placebo [69].

Addition of hypoglycemic agents with antihypertensive effects should be done cautiously in hypertensive diabetics well controlled on antihypertensives. The need may arise to reduce the doses of antihypertensive drugs. Patients should be warned about the blood pressure lowering effects of these drugs.

Antihypertensive Medications

Medication classes used to treat HTN:

- ACEI (ACE inhibitor)
- ARB (angiotensin receptor blocker)
- CCB (calcium channel blocker)
- Diuretics
- Alpha/beta-adrenergic blockers
- Beta-adrenergic blockers
- Alpha blockers
- Alpha-2 agonists
- Mineralocorticoid receptor (MR) blockers
- Vasodilators
- Renin inhibitors

When initiating pharmacotherapy for the treatment of HTN, it is important to consider patient characteristics, medication tolerability, and desirable protective effects. The preferred initial medication according to the ADA and AACE/ACE is a RAAS blocker (ACEI or ARB) in patients with DM due to the beneficial effect on cardiovascular outcomes. If BP is not controlled, other classes of medications should be added until goal BP is obtained [4]. Evidence including systematic reviews and meta-analysis has shown that RAAS blockers not only are comparable to other classes of medications in efficacy for treatment of HTN but also reduce the risk of microalbuminuria and creatinine doubling. This suggests that RAAS blockers may be preferred to other antihypertensive agents, as it is well documented that both HTN and DM are associated with the development of CKD [70, 71]. The combination of an ACEI and ARB is not recommended, as they were associated with increased risk of hypotension, syncope, and renal failure in Ongoing Telmisartan Alone and in combination with Ramipril Global enspoint Trial (ONTARGET) [56]. In the JNC 8 guidelines, there was no preference given to a particular agent, and it was recommended that a thiazide-type diuretic, CCB, ACEI, or ARB be used as the initial antihypertensive medication. These guidelines were derived solely from RTCs, which are considered the gold standard for evidence-based medicine [9].

Amlodipine, a CCB, has been compared to other medications in large-scale clinical trials in patients with DM and HTN. The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial compared the combination of benazepril/amlodipine to benazepril/hydrochlorothiazide and found a 21% relative risk reduction in cardiovascular events with the amlodipine-containing combination. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) found a 14% reduction in cardiovascular events with amlodipine compared to atenolol. CCBs are well tolerated, do not have unfavorable effects on metabolism, and may be the best medication to add to a RAAS blocker if combination therapy is required to reach BP goals in the diabetic population [72].

Diuretics, in particular the thiazide-type diuretics, are a common first choice for the treatment of HTN; however, there are some disadvantages to their use in the diabetic population. They can cause metabolic derangements such as hyperuricemia, dyslipidemia, insulin resistance, and hyperglycemia. Despite these side effects, diuretics have been shown to be as effective as CCBs and ACEIs in decreasing the risk of CVD events and have a significant role in the treatment of HTN in DM [72].

Beta-blockers have been associated with metabolic derangements including dyslipidemia, increased insulin resistance, and weight gain. Beta-blockers can mask hypoglycemia symptoms. Like diuretics, beta-blockers have a significant role in the treatment of HTN in DM, particularly when patients have had a previous myocardial infarction, rhythm disorder, or heart failure. The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial studied patients already on a RAAS blocking agent. Results suggested that if a beta-blocker is indicated, carvedilol might be superior to metoprolol as it was not associated with the increase in hemoglobin A1c or dyslipidemia that was seen with metoprolol [72, 73].

Combination therapy is often necessary in diabetics with HTN and lead to more patients achieving goals when compared to monotherapy, regardless of the baseline BP. In the UKPDS study, three or more medications were required to achieve goals in up to one third of patients [74]. It was the recommendation of the JNC 7 that if BP was more than 20 systolic and more than 10 mmHg diastolic above goal that combination therapy be initiated [75].

When patients are not at goal on optimal doses of three antihypertensive agents including a diuretic, it is referred to as resistant HTN. Resistant HTN is common in patients with diabetes and obesity. Secondary causes of HTN should be

excluded and referral to a HTN specialist should be considered in resistant cases. There is a hypothesis that resistant hypertension occurs due to excess sodium retention. Thus, additional diuretic action by adding a mineralocorticoid receptor (MR) blocker may be beneficial. Spironolactone and eplerenone are steroidal MR blockers, and the newer Finerenone is a nonsteroidal MR antagonist. Since Eplerenone and Finerenone are more selective mineralocorticoid receptor blockers, they are not associated with gynecomastia and menstrual irregularities seen with spironolactone. A study showed that spironolactone was superior to placebo, doxazosin, and bisoprolol in patients with resistant HTN; however, this was not done in a solely diabetic population, and patients with CKD with a GFR <45 mL/min were excluded. MR blockers should be used cautiously, as they can lead to hyperkalemia, especially in the DM population, in which CKD is more common [76]. In the Finerenone trial for reducing kidney failure and disease progression in diabetic kidney disease (FIDELIO- DKD) showed that when finerenone is added to treatment of patients with CKD and type 2 diabetes already on maximum tolerable doses of renin angiotensin system blockers it resulted in lower risks of CKD progression and cardiovascular events than placebo [77]. Finerenone is indicated to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, nonfatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 DM.

Aliskiren is the only renin inhibitor out in the market. It is an effective antihypertensive agent that is well tolerated. In the air versus oxygen in myocardial infraction trial (AVOID), Aliskerin plus losartan showed a 20% greater reduction in proteinuria compared to losartan and placebo. This study showed that the reno protective effect of Aliskerin was independent of the BP lowering effect in diabetic and hypertensive patients with nephropathy on losartan [78]. The Aliskiren Trial in Type 2 Diabetes using Cardiorenal end points (ALTITUDE) was done to determine the safety and effectiveness of direct renin inhibitors compared with placebo with respect to fatal and nonfatal renal and cardiovascular events in patient with type 2 diabetes who were on an ACE inhibitors or ARB. This study did not show a statistically significant difference in cardiovascular events with addition of Aliskerin, but the addition of Aliskerin caused a higher incidence of hyperkalemia and hypotension [79]. At his point, addition of Aliskiren to ACE inhibitor and ARB therapy is not recommended (Fig. 39.3).

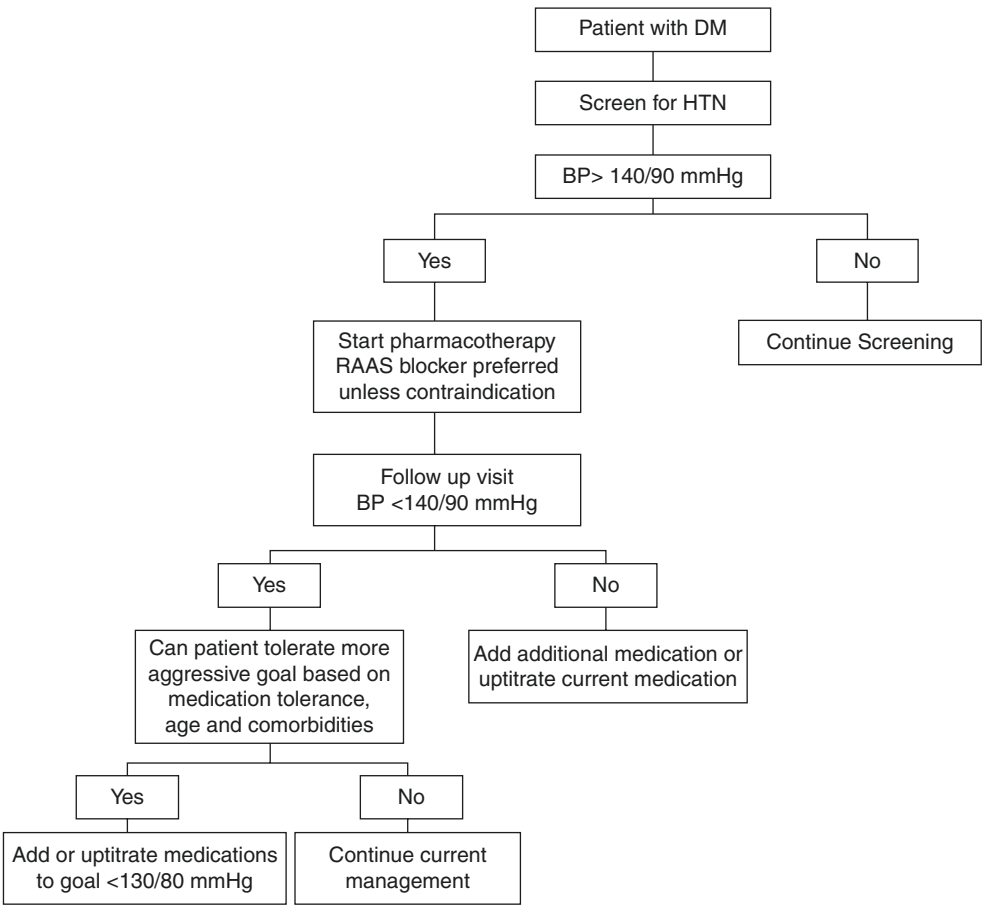

Fig. 39.3 Flow chart for the treatment of HTN in diabetes

Other Monitoring Modalities

Screening and monitoring of treatment for HTN has traditionally been based on evaluation in the healthcare setting. Out-of-office BP monitoring has been used in European guidelines; as of April 2021, the US Preventive Services Task Force (USPSTF) has endorsed its use for diagnosis and management of HTN. Ambulatory BP monitoring (ABPM) involves placement of a BP cuff on the nondominant arm that measures BP over the course of a 24-h period by taking measurements every 15–30 min. Compared to in-office BP measurement, ABPM is of higher prognostic value for CKD, CVD, and mortality risks [80].

Suspected white coat HTN, evaluation of resistant HTN, episodic HTN, suspected episodes of hypotension, and evaluation of treatment efficacy are indications for ABPM. Patients with DM who have BP excursions on 24-h monitoring are at increased risk of complications even before the diagnosis of HTN. Both Type 1 DM and Type 2 DM in comparison with controls without DM have been found to have higher mean BP values. These elevated means were associated with higher rates of nephropathy, albuminuria, retinopathy, and increased left ventricular mass. BP normally has a physiologic circadian rhythm in which BP drops >10% during the night relative to daytime BP. Patients in which BP decreases by <10% are said to have a non-dipping pattern, which was observed to be more prevalent in those with DM. This non-dipping pattern has been associated with cardiovascular autonomic neuropathy; its contribution to progression of chronic DM complications however is more controversial. Studies thus far have shown some mixed results and may be more relevant and add information to other BP values when related to outcomes with retinopathy. Hyperglycemia has exhibited a role in normal nocturnal BP fall, likely related to its effect on modifying circulating plasma volume, interfering with blood flow distribution and renal hemodynamics. Decreased BP means and increased BP fall during the night have been seen after 1 week of improved glycemic control in type 1 DM. Patients with normal office BP measurements (<140/90 mmHg) with elevated ABPM measurements (>135/85 mmHg) are referred to as having masked HTN. Type 2 DM patients have been shown to have a higher prevalence of masked HTN at 30% versus 10–20% in those without DM. Masked HTN has been associated with increased cardiovascular risk and when studied in Type 2 DM patients was associated with albuminuria and increased left ventricular wall thickness. ABPM appears to add significant information that can be used in risk stratification in the DM population and should be utilized more frequently. However, additional clinical study is needed to further explore the parameters obtained with ABPM and their effects on the complications of DM and to develop treatment strategies to benefit such patients [81].

PWV is a noninvasive measure of arterial stiffness with carotid-femoral PWV considered the reference standard measurement of aortic stiffness. It is not used clinically in the United States; however, it is suggested in Europe by expert consensus that carotid-femoral PWV greater than 10 m/s is a cardiovascular risk factor for middle-aged adults with HTN. Studies have shown an association between DM and aortic stiffness measured by PWV, which did not vary by gender but was significantly stronger in Caucasians as compared to African Americans. In more advanced DM, present for more than 10 years, albuminuria and elevated glycosylated hemoglobin were all associated with higher aortic stiffness measured by PWV. This suggests that PWV measurement may contribute to the currently available methods to risk stratify patients who have more risk of developing cardiovascular events and mortality related to complications of DM. However, further clinical studies are needed to help delineate how this modality for the measurement of arterial stiffness can specifically be used in the diabetic population and if treatment targeting arterial stiffness can improve outcomes [82].

COVID-19 and Antihypertensive Therapy in Individuals with Diabetes

The ongoing novel SARS-CoV-2 coronavirus (COVID-19) pandemic has had a disproportionate impact on individuals with multiple medical comorbidities. For instance, a large observational study from China revealed that up to 23.7% of patients with severe infection had a history of hypertension and 16.2% were known diabetics compared to patients with nonsevere infection of whom just 13.4% and 5.7% had a history of hypertension and diabetes, respectively [83]. Likewise, studies in the United States have shown as much as 78% of patients admitted to ICU with COVID-19 have diabetes and that diabetics are more than twice as likely as nondiabetics to get admitted to a hospital with COVID-19 after adjusting for other comorbidities [84]. It is now believed that diabetic individuals have an exaggerated immune response to infection with COVID-19 leading to increased production of inflammatory cytokines and reactive oxygen species. This cascade ultimately results in greater end organ injury and excess mortality [85]. These individuals also have a higher prevalence of heart failure and chronic kidney disease that predispose to complications from COVID-19. Moreover, it has been observed that many patients with hypertension and diabetes share common underlying socioeconomic themes such as lack of access to quality healthcare and healthy foods that increases their risk for adverse outcomes [86].

Extensive research into COVID-19 infection in this subset of patients has led to questions on the role of ACE inhibi-

tors and ARBs in its pathogenesis. Specifically, the observation that the novel coronavirus binds to human cells via the angiotensin-converting enzyme 2 raised concerns that medications such as ACE inhibitors and ARBs might accelerate infection with the novel coronavirus by increasing the levels of this enzyme. However, currently, there is no clinical evidence to support this hypothesis. The European Society of Cardiology Council on Hypertension, the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) and the American Society of Hypertension have all released policy statements strongly recommending that patients continue treatment with their usual antihypertensive regimen [87]. Therefore, at this time, recognizing the multiple benefits obtained with these classes of medications in patients with diabetes and hypertension, it is not advisable to discontinue therapy simply because of COVID-19 infection [88].

Future Considerations

There should be more awareness about HTN complicating diabetes. Healthcare systems should have more aggressive screening to diagnose these conditions. Every new hypertensive patient should be screened for diabetes. Lifestyle modifications are the cornerstone for management of these two interrelated medical conditions and should be emphasized at a younger age. Schools should have more programs that advocate healthy living.

Most of current HTN studies are based on office BP monitoring. ABPM and home BP monitoring should be used more frequently. This technique is a very useful tool in white coat HTN (high BP in clinic but normal in other settings) and masked HTN (normal BP in clinic and high BP at other settings). Additionally, it is also helpful in resistant HTN, episodic HTN, autonomic dysfunction, and hypotension while taking antihypertensive medications. ABPM also identifies patients who have nocturnal HTN dipper versus non-dippers. This has important implications since non-dippers are at higher cardiovascular risk. Some experts believe that home BP monitoring should be done several times a day and dosage of BP medications adjusted based on BP at a given time similar to finger stick blood glucose monitoring and adjustment of insulin dosing.

There should be more American Society of Hypertension certified HTN centers that are focused on treating patients who have more complex issues with HTN and related complications so that patients can be referred to these centers for more comprehensive care. Internal medicine and related residency and fellowship training programs should encourage more trainees to become hypertension specialists. More research should be done on genetic analysis to provide more individualized medicine, which will help determine the appropriate medication/medications for any given patient. The low efficacy of some therapies could be related to interindividual genetic variability. Genetic studies of families have suggested that heritability accounts for 30–50% of interindividual variation in blood pressure (BP). Genome-wide studies have confirmed that genetic factors are related not only to BP elevation but also to interindividual variability in response to antihypertensive treatment. Due to the polygenic nature of hypertension, a single locus cannot be used as a relevant clinical target for all individuals. Therefore, the analysis of complex traits, such as drug response phenotypes, should involve the assessment of interactions among multiple loci. Genome-wide association studies (GWASs) have led to the discovery of variants associated with drug efficacy and adverse drug reactions. However, due to the multigenic and multifactorial nature of the drug response phenotypes, further research in this area is required to establish reliable recommendations [89].

Conclusion

Over 20 million people in the United States have both HTN and DM. Diagnosis and treatment of these conditions is very important to decrease the risk of CVD, which is a major cause of morbidity, mortality, and healthcare cost. The pathophysiology of HTN in DM is complex with the inappropriate activation of the RAAS system, the endocrine action of adipose tissue, oxidative stress, and maladaptive effects on the vascular endothelium being involved. The western diet and obesity play an important role in inducing a pro-inflammatory state contributing to metabolic derangement. There have been multiple large-scale clinical trials that have examined BP control in DM and its effect on CVD outcomes. The data from these studies suggests that targeting a systolic BP between 120 mmHg and 135 mmHg would be most appropriate, reserving a more aggressive target of <120/80 mmHg in select patients that are at highest risk of stroke and can tolerate the target without adverse effects. Lifestyle modification remains the most important intervention including a reduced sodium diet, weight loss, exercise, and moderation of alcohol intake. When treating DM in patients with HTN, it is important to note that the choice of DM medications can have an impact on BP control. ACEI or ARB should be considered preferred initial therapy for diabetics with HTN due to beneficial effect on CVD and renal outcomes. Adding medications or titrating existing medications should be done until BP goals are met. ABPM should be used for further evaluation in cases of resistant HTN, episodic HTN, and suspected white coat HTN or episodes of hypotension. PWV may be an additional tool that can be used to identify patients at risk for developing CVD and complications of DM. There continues to be further studies contributing to the knowledge of these interrelated conditions.

Concluding Remarks: Diabetes and hypertension are frequent co-existing risk factors that are promoted by obesity and increase the risk for both CVD and CKD. There is increasing evidence that treatment of both conditions should be individualized based on various factors such as age and duration of diabetes. Emerging evidence suggests that an optimal goal for blood pressure control is less than 130/85 mmHg for most patients with diabetes.

Multiple Choice Questions

1. Which one of the following studies showed that combination of angiotensin converting enzyme inhibitor and angiotensin receptor blockers were associated with and increased risk of renal failure?
   (a) UKPD
   (b) **ONTARGET**
   (c) ADVANCE
   (d) VADT
   (e) SPRINT

   The ONTARGET trial-Ongoing Telmisartan Alone and in combination with Ramipril global endpoint trial showed that the combination was associated with increased risk of hypotension, syncope, and renal failure.
2. Ambulatory BP monitoring will be helpful in all the following conditions except:
   (a) 45 year with uncontrolled HTN on maximum dose of three medications including a diuretic
   (b) **60 year old with well-controlled HTN on 2 BP medications**
   (c) 35 year with good BP at home and local store but high at the physician office
   (d) 45-year-old diabetic who complains of orthostatic symptoms
   (e) To evaluate masked HTN (normal office BP with elevated Home BP)

   Ambulatory BP monitoring should be considered in suspected white coat HTN, resistant HTN, episodic HTN (i.e., pheochromocytoma), autonomic dysfunction, or suspected episodes of hypotension.
3. All of the following antidiabetic medications will lower BP except:
   (a) Exanetide
   (b) Sitagliptin
   (c) Pioglitazone
   (d) Empagloflozin
   (e) **Insulin.**

   Antidiabetic medications GLP-1 agonists, DPP4 inhibitors, SGLT-2 inhibitors, Bromocriptine mesylate QR, and thiazolidinediones have shown to reduce BP.
4. All of the following are true about DASH diet except:
   (a) Has as a positive impact on BP
   (b) DASH diet is high in whole grains, fish, poultry, fruits, and vegetables
   (c) Has shown to reduce cardiovascular risk
   (d) **Has been shown to increase pulse wave velocity**
   (e) DASH diet will lower LDL cholesterol

   DASH diet has shown a positive impact on BP, obesity, and LDL cholesterol. DASH diet has also been shown to reduce cardiovascular risk and reduce pulse wave velocity.
5. When treating diabetics with HTN, which of the following is correct?
   (a) **American Diabetic Association and American Association of Clinical Endocrinologists recommend RAAS blockers as first line treatment.**
   (b) JNC 8 recommends a BP goal of less than 120/80 for all diabetics.
   (c) Use of thiazide diuretics are not recommended due to associated metabolic derangements.
   (d) Metoprolol is preferred over carvedilol.
   (e) There is no additional benefit of using RAAS blockers over other antihypertensives.

   AACE and ADA recommend RAAS blockers as the first line of treatment for diabetics due to beneficial effects on cardiovascular outcome. In addition, it reduces microalbuminuria and the risk of creatinine doubling. JNC 8 recommends a BP goal of <140/90. Despite metabolic derangements associated with thiazide diuretics, they are still used to treat diabetics. Diuretics have shown to reduce cardiovascular risk. Unlike metoprolol, carvedilol will not increase blood sugar or lipids.
6. The 2020 Canadian HTN guidelines recommend that newly diagnosed patients with HTN be screened for which of the following cardiovascular risk factors?
   (a) Kidney disease
   (b) Dyslipidemia
   (c) Diabetes mellitus
   (d) b and c
   (e) a, b and c.

   The 2020 Canadian HTN guidelines recommend that newly diagnosed patients with HTN be screened for diabetes with a fasting glucose and/or hemoglobin A1c, as well as hyperlipidemia with labs for serum total cholesterol, LDL, HDL, non-HDL cholesterol, and triglycerides, as well as kidney disease with urinalysis, assessment of albumin excretion in diabetics.
7. What is the initial weight loss goal from baseline weight in the National Institutes of Health clinical guidelines for treatment of obesity?
   (a) 5%
   (b) 20%
   (c) 30%
   (d) **10%**
   (e) 25%

Approach to weight loss and maintenance based on National Institutes of Health clinical guidelines for treatment of obesity recommends an initial weight loss goal of a 10% reduction from baseline weight.

8. All of the following are nondesirable side effects of beta blockers in diabetics except:
   (a) Masking of hypoglycemia symptoms
   (b) **Lowering of heart rate**
   (c) Dyslipidemia
   (d) Weight gain
   (e) Insulin resistance

   Beta-blockers have been associated with metabolic derangements including dyslipidemia, increased insulin resistance, and weight gain and can mask hypoglycemia symptoms.
9. The following have been postulated to be involved in the pathophysiology of HTN in DM except:
   (a) Sodium retention due to hyperfiltration
   (b) Reduced nitric oxide bioavailability
   (c) Deranged metabolic signaling of insulin.
   (d) **Reduced sympathetic nervous system activation**
   (e) Inappropriate activation of the RAAS system

   The pathophysiology of HTN in DM is multifactorial, involving multiple tissues, organ systems, metabolic signaling pathways, and environmental and genetic factors.
10. Lowering systolic BP to less than what number was shown in multiple major trials to lower mortality and improves CVD outcomes?
    (a) 160
    (b) **150**
    (c) 140
    (d) 130
    (e) 120

    Major trials such as Syst-Eur, UKPDS, and SHEP studies supported the conclusion that treatment to a systolic BP of <150 mmHg lowers mortality and improves CVD and cerebrovascular health outcomes.
11. All of the following statements are true of finerenone except
    (a) It is a non-steroidal mineralocorticoid receptor antagonist
    (b) Contraindicated in patients with adrenal insufficiency
    (c) **Best taken on an empty stomach**
    (d) Only Mineralocorticoid receptor antagonist indicated to reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death, nonfatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes
    (e) No relevant affinity to androgen, progesterone, and estrogen receptors

Finerenone is a nonsteroidal mineralocorticoid receptor blocker that can be taken with or without food. It is contraindicated in adrenal insufficiency and with concomitant use with strong CYP3A inhibitors. It is the only MR blocker indicated to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, nonfatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes. No relevant affinity to androgen, progesterone, and estrogen receptors. It can be taken with or without food.

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Further Reading

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Diabetes and Atherogenic Dyslipidemia

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Arshag D. Mooradian

Introduction

Despite the recent decline in the incidence of cardiovascular mortality in people with diabetes, cardiovascular disease (CVD) continues to be the leading cause of morbidity and mortality in this patient population [1–5]. The cause of accelerated atherosclerosis and premature emergence of coronary artery disease (CAD) is multifactorial. Nevertheless, dyslipidemia is an important risk factor in diabetes that is modifiable with lifestyle changes and institution of effective pharmacologic agents [6, 7].

People with diabetes can have all the variants of dyslipidemias observed in nondiabetic people [7–9]. However, in type 2 diabetes where obesity and insulin resistance are common, a typical dyslipidemia is manifested as high plasma triglyceride and low high-density lipoprotein (HDL) cholesterol concentrations and increased small dense low-density lipoprotein (LDL) cholesterol particles [8, 9].

Prevalence of Dyslipidemia in Diabetes

In the Framingham Heart Study, the prevalence of high LDL cholesterol concentrations in men and women with diabetes mellitus (9% and 15%, respectively) did not differ significantly from the rates in men and women who did not have diabetes (11% and 16%, respectively) [10]. However, people with diabetes had more often high plasma triglyceride concentrations (19% in men and 17% in women) than people without diabetes mellitus (9% of men and 8% of women). In this survey, high levels of total cholesterol, LDL cholesterol, and triglyceride were defined as values above the corresponding 90th percentile for the US population [10]. The prevalence of low plasma HDL cholesterol concentrations (defined as a value below the 10th percentile for the US population) was 21% in men and 25% in women with diabetes, while only 12% nondiabetic men and 10% of nondiabetic women had low HDL cholesterol levels [10]. A similar increase in the prevalence of hypertriglyceridemia and low HDL cholesterol level was observed in the UK Prospective Diabetes Study (UKPDS) [11].

Pathophysiology of Dyslipidemia in Diabetes

One of the major drivers of increased plasma triglyceride concentrations in people with type 2 diabetes is the increased free fatty-acid release from insulin-resistant fat cells [7–9]. The increased flux of free fatty acids into the liver promotes triglyceride production. Subsequently, there is increased secretion of apolipoprotein B (apoB) and very low-density lipoprotein (VLDL) cholesterol.

Insulin resistance is also associated with low HDL cholesterol levels [7–9] and increased concentration of small dense LDL-cholesterol particles as VLDL-transported triglyceride is exchanged for HDL or LDL-transported cholesteryl ester through the action of the cholesteryl ester transfer protein (CETP) (Fig. 40.1). This exchange results in increased amounts of both atherogenic cholesterol-rich VLDL remnant particles and triglyceride-rich, cholesterol-depleted HDL and LDL particles. The latter triglyceride-enriched particles are hydrolyzed by hepatic lipase or lipoprotein lipase resulting in dissociated apolipoprotein A-I (apo A-I) that is filtered by the renal glomeruli and degraded in renal tubular cells (Fig. 40.1) [7–9]. The increased concentration of small dense LDL-cholesterol particles occurs by a similar lipid exchange that results in lipid depletion of the LDL particles (Fig. 40.1).

The lipid exchange pathway cannot entirely explain why low HDL cholesterol levels can also occur in people who do not have hypertriglyceridemia. In these patients, inability of insulin to upregulate the apo A-I production owing either to insulin resistance or increased inflammatory cytokines notably tumor necrosis factor (TNF) alpha might contribute to low HDL cholesterol levels [12–14].

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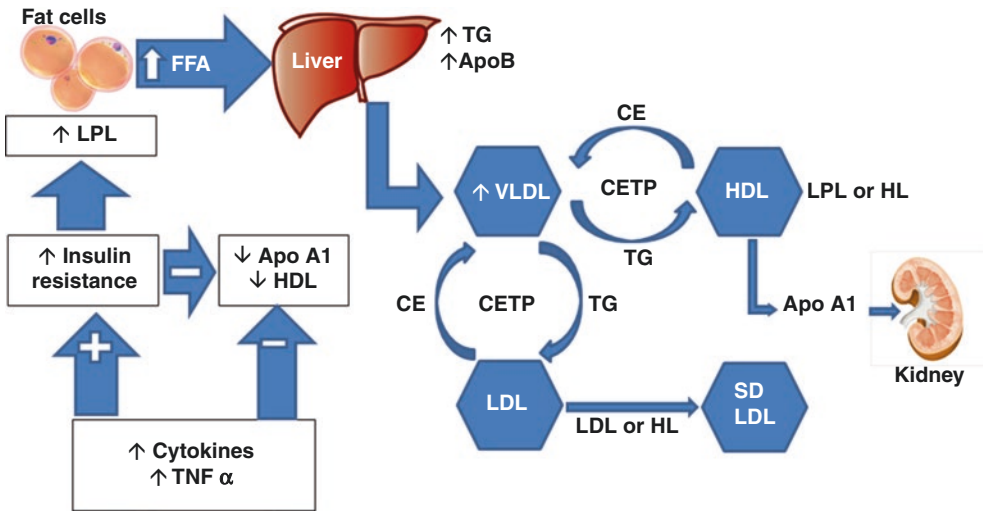

Fig. 40.1 Pathogenesis of diabetic dyslipidemia. Insulin resistance initiates the characteristic triad of high triglyceride level, low HDL cholesterol level, and high small dense LDL level. If the concentration of VLDL transported triglyceride is high, CETP promotes the transfer of LDL cholesteryl ester or HDL cholesteryl ester in exchange for triglyceride. Triglyceride-rich HDL or LDL can undergo hydrolysis by hepatic lipase or lipoprotein lipase. ↑ increased level, *TNF α* tumor necrosis factor α, *ApoA-1* apolipoprotein A-1, *ApoB* apolipoprotein B, *CE* cholesteryl ester, *CETP* cholesteryl ester transfer protein, *FFA* free fatty acid, *HL* hepatic lipase, *LPL* lipoprotein lipase, *SD LDL* small dense LDL cholesterol, *TG* triglyceride, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *VLDL* very low-density lipoprotein. Reprinted from reference [8] with permission of the authors and the publisher

Insulin resistance is also associated with a decreased ratio of lipoprotein lipase to hepatic lipase in heparin-treated plasma, which contributes to the low HDL-cholesterol level [8, 9]. In addition, the esterification of cholesterol (mediated by lecithin-cholesterol acyl transferase) is either modestly increased or unaltered, whereas increased CETP activity depletes HDL of its cholesteryl ester and therefore contributes to the lowering of HDL cholesterol levels [8, 9].

It is noteworthy that the combination of high triglyceride and low HDL cholesterol levels is observed in familial and sporadic syndromes (e.g., familial combined hyperlipidemia and familial hypertriglyceridemia) and the onset of obesity and insulin resistance would augment the lipid abnormality phenotype in these people [9].

Atherogenicity of Dyslipidemia in Diabetes

Interventional trials with statins have proven the efficacy of these drugs in reducing cardiovascular events in people with diabetes. In these trials, the linear relationships between LDL cholesterol levels and the incidence of cardiovascular events were similar in individuals both with and without diabetes mellitus [15]. However, the role of low HDL cholesterol and increased triglyceride levels in CVD is still unproven. The association between hypertriglyceridemia and the increased risk of CVD is not as strong as the association between LDL cholesterol level and CVD risk.

Patients with elevated triglyceride levels especially in the context of familial combined hyperlipidemia or low HDL level might have increased risk for CVD. In addition, severe hypertriglyceridemia (greater than or equal to 5.65 mmol/L (500 mg/dL) increases the risk of pancreatitis.

Interventional trials that used fibrate therapy to lower triglyceride and increase HDL cholesterol levels have failed to show a reproducible reduction in cardiovascular events. In the HDL Intervention Trial (HIT), gemfibrozil treatment was associated with a 22% reduction in the risk of coronary heart disease (CHD) and a 25% reduction in the risk of stroke [16]. In the latter study, a quarter of the subjects studied had diabetes. The favorable effect of gemfibrozil in the primary prevention of CHD was also demonstrated in previous trials [17].

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study did not show that fenofibrate had a statistically significant effect on the primary outcome (CHD-related death or nonfatal myocardial infarction) [18, 19]. However, fenofibrate reduced the prevalence of nonfatal myocardial infarction and coronary revascularization, but it did not reduce the risk of fatal events [18, 19].

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study examined whether treatment with a statin plus a fibrate, as compared with statin alone, would decrease the risk of cardiovascular events in a population of 5518 patients with type 2 diabetes [20]. After a mean follow-up period of 4.7 years, fenofibrate with simvastatin group compared with simvastatin alone did not have reduced cardiovascular events. Further analyses suggested a possible benefit for patients with the combination of a high baseline triglyceride level and low HDL cholesterol [20]. This observation

was in agreement with the previous findings in the FIELD trial [19].

The HDL has a central role in reverse cholesterol transport and possesses a number of other cardioprotective properties. However, most trials with agents known to increase HDL levels have not shown any reduction in cardiovascular events except possibly in a subgroup of patients with high serum triglycerides and low HDL cholesterol levels [21–26].

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides Impact on Global Health Outcomes (AIM-HIGH) [21] and the Heart Protection Study 2: Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) [22] used niacin as the HDL cholesterol-boosting agent. Four clinical trials used CETP inhibitors to increase HDL cholesterol level [23–26]. Only the Randomized Evaluation of the Effects of anacetrapib through Lipid Modification (REVEAL) trial showed favorable effects on cardiovascular outcomes, but most of the benefit was attributed to its ability to reduce non-HDL cholesterol levels [26]. It is possible that when HDL levels are increased with enhanced de novo production rather than impaired turnover secondary to CETP inhibition, the quality and functionality of HDL improve to become a more effective cardioprotective moiety [27].

Management of Dyslipidemia in Diabetes Mellitus

An integral component of the management of dyslipidemia is to exclude secondary aggravating causes notably hypothyroidism and use of hormone replacement therapy. Although most people with diabetes would require pharmacologic agents, lifestyle modifications are still important cornerstone of therapy. These include dietary restrictions, increased physical activity, and smoking cessation [7]. Glycemic control usually improves the dyslipidemia by either providing insulin or enhancing insulin action, but it may not increase the reduced HDL cholesterol levels [28]. In addition, some agents such as pioglitazone may have direct effects on lipid metabolism [8].

Medical Nutrition Therapy

Dietary interventions should be individualized based on patient's own dietary preferences [8, 9]. While the low fat diet has been the cornerstone of the dietary guidelines in the past, more recent guidelines emphasize the importance of limiting added sugars to less than 10% of total energy intake. This recommendation is based on a large body of evidence for the association between the consumption of added sugars, especially fructose from corn syrup and atherogenic lipid profile [29–32]. In addition, clinical trials using a diet enriched with monounsaturated fat such as the Mediterranean diet have shown favorable effects on cardiovascular risk [33]. When weight loss is the goal of dieting, there is not clinically meaningful difference between carbohydrate-restricted diets and fat-restricted diets. It is best to limit portion size as all calories count irrespective of their source [32, 34]. The American Diabetes Association (ADA) recommends modest weight loss for overweight individuals [35]. As little as 5% weight loss can have favorable metabolic effects, and clinical studies have shown that 7% or less of weight loss can prevent or delay the onset of diabetes in high-risk individuals [36].

Low-carbohydrate diets (LCD) can enhance weight loss in the short term although its effect is small and not sustainable [32]. In people with diabetes and insulin resistance, LCD is helpful in achieving glycemic control. However, there are untoward side effects especially when carbohydrates are severely restricted (<50 g/day) to induce ketosis. The latter curbs appetite but also may cause nausea, fatigue, and water and electrolyte losses and limits exercise capacity [32]. In addition, observational studies suggest that low-carbohydrate diets (<40% energy from carbohydrates) as well as very high carbohydrate diets (>70% energy from carbohydrate) are associated with increased mortality [32]. The available scientific evidence supports the current dietary recommendations to replace highly processed carbohydrates with unprocessed carbohydrates as well as limiting added sugars in the diet [32].

The type of fat consumed is more important than total amount of fat. A reduction in dietary saturated fat to less than 10% of total daily calories is recommended along with preferential consumption of monounsaturated fat, elimination of trans-fat intake, and limiting daily sodium consumption to less than 2300 mg [35]. Overall, Mediterranean [33] or Dietary Approaches to Stop Hypertension (DASH) [37] style diets are prudent advice to people with diabetes. Of note is that the previous recommendation of restricting dietary cholesterol intake to less than 300 mg/day has been removed from the 2015 and 2020 Dietary Guidelines for Americans [29]. People with diabetes should follow the dietary guidelines issued for the general population [35].

It is noteworthy that replacing saturated fat intake with carbohydrate lowers total cholesterol, LDL and HDL cholesterol, and may increase triglyceride level [38, 39]. On the other hand, substituting saturated fat with monounsaturated or polyunsaturated fat has favorable effect on HDL cholesterol and triglyceride levels. Dietary protein or various amino acids do not have clinically significant effects on lipoprotein profile [38, 39].

Effects of Exercise

Staying active and exercising have multiple benefits notably enhanced cardiovascular health. Increased physical activity also helps to maintain the weight loss attained with caloric restriction [40]. In addition, independent of weight loss, exercise can improve insulin sensitivity and increase HDL cholesterol levels [41, 42]. Both aerobic or resistance training improve glycemic control in type 2 diabetes, and larger improvement in glycemic control can be achieved with combined resistance and aerobic training [43].

There is a paucity of trials examining the effect of exercise on lipid changes in diabetes. In a study of postmenopausal women with type 2 diabetes, exercise without weight loss was associated with a reduction in waist circumference and improve visceral adipose tissue [44]. In another study of people with type 2 diabetes, a supervised aerobic exercise program reduced VLDL–apo B pool size [45]. Despite the limitations in these studies, it is a prudent clinical practice to encourage people with diabetes to engage in exercise to the extent possible. Overall, 30 min of walking five times a week is effective in improving insulin sensitivity and reducing the risk of diabetes in those at risk for developing diabetes [36].

Pharmacologic Interventions

Various classes of lipid-modifying agents are summarized in Table 40.1. Of these agents, statins have been consistently associated with cardiovascular event reduction [15]. Although the efficacy of statins correlates well with their ability in reducing LDL cholesterol, the potential contribution of pleiotropic effects of statin to CVD risk reduction was supported by the observation that therapeutic targeting hsCRP (highly sensitive C-reactive protein) with rosuvastatin was associated significant improvement in event-free survival, and the effect was independent of LDL cholesterol level achieved [46].

The cholesterol hypothesis in contrast to the statin hypothesis is supported by the observation that ezetimibe, a selective cholesterol absorption inhibitor, was also associated with reduction in CVD events when used in addition to statins [47]. This latter study is in contrast to earlier studies with ezetimibe, one in patients with aortic stenosis [48] and the other in those with chronic kidney disease [49]. In the latter studies, ezetimibe and statin combination did not alter mortality but had some favorable effects on secondary endpoints such as fewer coronary bypass procedures, reductions in non-hemorrhagic stroke, and arterial revascularization procedures [48, 49]. Thus, ezetimibe should be considered when maximal doses of high potency statins are not tolerated [35]. Similarly, two interventional trials with PCSK9 (proprotein convertase subtilisin/kexin 9) inhibitors, evolocumab and alirocumab, showed a reduction in cardiovascular events in a high-risk population with LDL cholesterol levels of 1.8 mmol/L (70 mg/dL) or higher who were receiving statin therapy [50, 51]. Another related drug soon to be available is inclisiran (Leqvio®). This investigational drug would be the first LDL cholesterol-lowering siRNA medicine. Its twice-yearly dosing by subcutaneous injection is a significant advantage in enhancing adherence to cholesterol lowering drugs [52].

An additional option is ATP citrate lyase inhibitor bempedoic acid (Nexletol®). This drug is approved for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL cholesterol. A single-pill combination of bempedoic acid and ezetimibe (Nexlizet®) is also available [53].

The bile acid sequestrants (BAS) have a limited role in reducing LDL cholesterol except possibly in women of reproductive age and children where safety of statins and ezetimibe is of concern. Gastrointestinal side effects, increased risk of cholelithiasis, and aggravation of hypertriglyceridemia limit the clinical utility of these agents. In general, colesevelam has a better gastrointestinal side effects profile and has favorable effects on glucose metabolism. In the glucose-lowering effect of WelChol Study (GLOWS) in patients with type 2 diabetes, colesevelam added to existing therapy with metformin- and/or sulfonylurea-lowered LDL cholesterol by 11.7% and HbA1c by 0.5% [54]. The increase in triglyceride level was not significant in the GLOWS, although in other trials, when colesevelam was added to sulfonylurea or insulin, the triglyceride levels increased by 17.7% and 21.5%, respectively ($P < 0.05$) [55–57].

Niacin lowers triglyceride, LDL cholesterol, and small dense LDL levels and raises HDL cholesterol. Thus, its pharmacologic effect is well suited to target the triad of diabetic dyslipidemia. However, the use of niacin has been limited by its side effects such as flushing, itching, gastrointestinal upset, tachycardia, hypotension, and aggravation of insulin resistance. More importantly, two large clinical trials, one the HPS-2 THRIVE and the second AIM-HIGH, failed to show any clinical benefit of adding niacin to statin therapy, and there was a possible increase in ischemic strokes with the combination therapy [21, 22]. The combination should rarely be used in patients with high risk of hypertriglyceridemia-related pancreatitis.

The role of fibrates is limited because of lack of reproducible cardiovascular benefits. However, results from the available clinical trials suggest that in the subgroup of patients with moderate dyslipidemia (high triglycerides ≥2.24 mmol/L (200 mg/dL) and low HDL cholesterol <0.9–1.0 mmol/L (35–40 mg/dL), fenofibrate treatment compared

Table 40.1 A select list of therapeutic agents available for the management of dyslipidemia

Drug or drug class	Pharmacologic effects	Side effects	Specific agents (trade name) and dosage
1. Single agent formulations			
HMG-CoA reductase inhibitors (statins)	LDL-c ↓ 18–55%	Hepatotoxicity, myopathy, risk of diabetes	Lovastatin (Mevacor®) 10–80 mg orally nightly or two divided doses
	HDL-c ↑ 5–15%		Lovastatin extended-release (Altoprev®) 10–60 mg orally nightly
	TG ↓ 7–30%		Lovastatin extended-release (Altocor®) 10–60 mg orally nightly
			Simvastatin (Zocor®) 5–80 mg orally nightly[a]
			Pravastatin (Pravachol®) 10–80 mg orally once daily
			Fluvastatin (Lescol®) 20–40 mg orally nightly
			Fluvastatin extended release (Lescol XL®) 80 mg orally up to a maximum daily dose 40 mg twice daily
			Atorvastatin (Lipitor®) 10–80 mg orally once daily
			Rosuvastatin (Crestor®) 5–40 mg orally once daily
			Pitavastatin (Livalo®) 1, 2, and 4 mg orally nightly
ATP citrate lyase inhibitor	LDL-c ↓ 17–24%	No major side effects	Bempedoic acid (Nexletol®, Nilemdo®) 180 mg orally once daily
	LDL-c ↓ 15–20%		
Ezetimibe	HDL-c ↑ 1%	No major side effects, rare myopathy	Zetia®, Ezetrol® 10 mg orally once daily
	TG ↓ 8%		
PCSK9 inhibitors	LDL-c ↓ 60%	Neurocognitive changes	Evolocumab (Repatha®) 140 mg SC Q 2 weeks or 420 mg Q month
	HDL-c ↑ 5%	Cost	Alirocumab (Praluent®) 75 mg SC Q 2 weeks or 150 mg Q month
	TG ↓ 15%		
Nicotinic acid (niacin)	LDL-c ↓ 5–25%	Flushing, hyperglycemia, hyperuricemia, hepatotoxicity	Nicotinic acid 1–2 g orally two or three times daily
	HDL-c ↑ 15–35%		Extended-release nicotinic acid (Niaspan®)
	TG ↓ 20–50%		1000–2000 mg orally nightly
	Small, dense LDL↓		Sustained-release nicotinic acid (Slo-Niacin®) 250–750 mg orally once or twice daily
			Other trade names include *B-3-50, B3-500-Gr, Niacin SR, Niacor, Niaspan ER, Neasyn-SR, Nialip, Nicocin ER*
Fibrates (fibric acid derivatives)	LDL-c ↓ 5–20%	Dyspepsia, gallstones, hepatotoxicity, myopathy	Fenofibrate, micronised (Antara™) 43 and 130 mg orally once daily
			Fenofibrate, micronised (Lofibra™) 67, 134 and 200 mg orally once daily
	HDL-c ↑ 10–35%		Fenofibrate (Tricor®) 48 and 145 mg orally once daily
			Fenofibric acid delayed release capsules (Trilipix®) 45 and 135 mg orally once daily
	TG ↓ 20–50%		Other trade names for fenofibrate include Fenoglide, Lipidil EZ, Lipidil Micro, Lipidil Supra, Lipofen, Triglide, Lipanthyl, Tricheck, Golip
			Gemfibrozil (Lopid®, Apo-Gemfibrozil®, Gen-Gemfibrozil®, PMS-Gemfibrozil®) 600mg orally twice daily Bezafibrate (Bezalip®, Bezagen®, Fibrazate®, Liparol™, Zimbacol®) 200 mg orally twice daily
	Small, dense ↓ LDL-c		Bezalip® Mono 400 mg orally once daily
			Pemafibrate (Parmodia®) 0.1–0.2 mg orally twice a day
Bile acid binding agents (or sequestrants)	LDL-c ↓ 10–20%	Gastrointestinal distress, constipation	Cholestyramine (Questran®, Prevalite®) 4–24 g orally two or three times daily
	HDL-c ↓ 1–2%		Colestipol (Colestid®) 5–30 g orally once or twice daily
	TG ↓ possible ↓ 10%		Colesevelam (Welchol®) 1.875–3.75 g orally once or twice daily

(continued)

Table 40.1 (continued)

Drug or drug class	Pharmacologic effects	Side effects	Specific agents (trade name) and dosage
Omega-3 fatty acid	TG ↓ 25–30%	Fishy aftertaste, gastrointestinal disturbances, possible association with frequent recurrences of atrial fibrillation or flutter	Lovaza® 2 g orally twice daily or 4 g once daily
	LDL-c ↓ 5–10%		OTC: e.g., fish oil, Promega, Cardio-Omega 3, Marine Lipid Concentrate, MAX EPA®, SuperEPA 1200, 2–4 g/day of EPA + DHA
	HDL-c ↑ 1–3%		*Epanova*® (*omega-3*-carboxylic acids) 2–4 g orally daily
			Vascepa® (icosapent ethyl) 4 g orally daily
2. Double agent formulations			
Simvastatin and Ezetimibe	LDL-c ↓ 45–60%	As above for individual agents	Ezetimibe/Simvastatin (Vytorin™) 10/10 mg,10/20 mg, 10/40 mg, and 10/80 mg orally once daily[b]
	HDL-c ↑ 6–10%		
	TG ↓ 23–31%		
Lovastatin and nicotinic acid	LDL-c ↓ 30–42%	As above for individual agents	Nicotinic acid/lovastatatin (Advicor®) 500/20 mg, 750/20 mg, 1000/20 mg, 1000/40 mg orally nightly
	HDL-c ↑ 20–30%		
	TG ↓ 32–44%		
Niacin extended-release/simvastatin	LDL-c ↓ 25%	As above for individual agents	Niacin extended-release/simvastatin (Simcor®) 500/20 mg to 2000/40 mg orally nightly
	HDL-c ↑ 24%		
	TG ↓ 36%		
	Non-HDL-c ↓ 27%		
Simvastatin and sitagliptin	LDL-c ↓ 20–40%	As above for statins	Simvastatin/sitagliptin (Juvisync®) 100/10 mg, 100/20 mg, 100/40 mg orally once daily
	HDL-c ↑ 5–10%		
	TG ↓ 10–20%		
	Hba1c ↓ 0.5–0.07%		
Atorvastatin and amlodipine	LDL-c ↓ 30–60%	As above for statins	Atorvastatin/amlodipine (Caduet®) 2.5, 5, or 10/10, 20, 40, or 80 mg orally once daily
	HDL-c ↑ or ↓ 5–10%		
	TG ↓ 30%		
	Anti-hypertensive		
Bempedoic acid and ezetimibe	LDL-c ↓ 30%	As above for individual agents	Bempedoic acid/ezetimibe (Nexlizet®) 180 mg/10 mg orally once daily

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DHA docosahexaenoic acid, *EPA* eicosapentaenoic acid, *HDL-c* high-density lipoprotein-cholesterol, *LDL-c* low-density lipoprotein-cholesterol, *OTC* over the counter, *TG* triglyceride
[a]The use of the 80 mg dose should be restricted to patients who have been taking simvastatin 80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity
[b]The use of the Vytorin™ 10/80-mg dose should be restricted to patients who have been on this strength chronically (e.g., for 12 months or more) without evidence of muscle toxicity

to placebo is associated with fewer cardiovascular events [19, 20]. Fibrate use can be considered in people with elevated triglyceride level >5.6 mmol/L (500 mg/dL) along with dietary modification and improving glycemic control to prevent chylomicronemia and the associated risk of pancreatitis. When used in combination with statins, fenofibrate or bezafibrate seems to convey a minimal risk of rhabdomyolysis, while the combination with gemfibrozil should be avoided. Pemafibrate (Parmodia®) is a novel selective peroxisome proliferator-activated receptor alpha (PPARα) modulator (or fibrate) that is currently available in Japan. The ongoing clinical trial, Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes (PROMINENT) (ClinicalTrials.gov Identifier: NCT03071692), will address the role of this fibrate in reducing cardiovascular events in people with diabetes [58].

Fish oil supplements are another option to reduce triglyceride levels. In general, daily supplements of 3–5 g of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) reduce serum triglyceride levels by an average of 28%. The Combination of Prescription Omega-3 Plus Simvastatin (COMBOS) trial in statin-treated patients who have persis-

tent triglyceride levels between 200 and 499 mg/dL found that omega-3 fatty acid supplementation reduced non-HDL-c by 9% compared with 2.2% with placebo, triglycerides by 30% compared to 6% with placebo, and increased the HDL cholesterol by 3.4% [59]. Two open-label trials suggested some clinical benefits of omega-3 fatty acids. In the Gruppo Italiano per lo Studio della Infarto Miocardico (GISSI-Prevenzione) trial, mortality was reduced by 28% in people with diabetes and by 18% in nondiabetics randomized to omega-3 fatty acid supplementation [60]. Similarly, in a study of Japanese hypercholesterolemic patients, daily supplementation with 1800 mg EPA was associated with a significant reduction in nonfatal coronary events [61]. However, in subsequent large cohorts of diabetic patients, fish oil supplementation was not associated with any beneficial outcomes [62–64]. These trials used 1 g of *n*-3 fatty acids. The subsequent Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) found an approximately 25% relative risk reduction ($p < 0.001$) in major adverse cardiovascular events with an ethyl ester form of eicosapentaenoic acid (EPA) (Vascepa®) 4 g/day compared with placebo after a median follow-up of 4.9 years [65]. These favorable cardioprotective effects were not duplicated in the trial with omega-3 carboxylic acids (Epanova®) as the STRENGTH (a long-term outcomes study to assess STatin Residual risk reduction with EpaNova in hiGh cardiovascular risk paTients with Hypertriglyceridemia) trial was terminated early for low likelihood of demonstrating a benefit. Nevertheless, it is approved for lowering triglycerides in patients with very high levels of triglycerides. This approval was based on data from a clinical development program that included positive results from the Phase III EVOLVE (EpanoVa fOr Lowering Very high triglyceridEs) trial [66].

In rare genetic disorders with sever hypercholesterolemia such as homozygous familial hypercholesterolemia, a novel antisense oligonucleotide inhibitor of apo B100 synthesis, mipomersen (Kynamro®), was developed, but its marketing and use has been discontinued because of significant risk of liver damage [67, 68].

Lomitapide (Juxtapid®), a microsomal triglyceride transfer protein (MTP) inhibitor reduces the synthesis of chylomicrons and very low-density lipoprotein, resulting in a reduction in plasma LDL levels. The drug was approved with a boxed warning for increased the risk of hepatotoxicity. Other precautions with lomitapide include reduced absorption of fat-soluble vitamins, gastrointestinal adverse events, and numerous drug–drug interactions [69].

Another medication for the treatment of homozygous familial hypercholesterolemia is evinacumab (Evkeeza®). This monoclonal antibody against angiopoietin-like 3 (ANGPTL3) acts as an inhibitor of lipoprotein lipase and endothelial lipase. In ELIPSE HoFH trial, individuals were treated with other lipid-lowering therapies, including maximally tolerated statins, PCSK9 inhibitors, ezetimibe, LDL apheresis, and lomitapide, adding evinacumab to other lipid-lowering therapies decreased LDL cholesterol by 49% on average, compared to lipid-lowering therapies alone. The drug's prohibitive cost will limit its utility [70, 71].

Another novel medication currently in clinical trials for the treatment of familial chylomicronemia syndrome is volanesorsen (Waylivra®). This is an antisense oligonucleotide inhibitor of apo C-III mRNA. In phase 2 trials, this agent resulted in 71% decrease in triglycerides, 46% increase in HDL cholesterol, and improved blood glucose levels in type 2 diabetes [72, 73].

There is emerging evidence that diabetes is associated with increased cellular stress notably, oxidative, inflammatory, and endoplasmic reticulum stress [74, 75]. These stressors promote atherosclerosis, and in two clinical trials with anti-inflammatory drugs, canakinumab [76] and colchicine [77] reduced major adverse cardiovascular events. Targeting cellular stress with novel and safe drugs may increase the opportunities for reducing cardiovascular events in people with diabetes.

A Rational Approach to Drug Therapy

The current consensus is to recommend high-intensity statin to all patients with diabetes and atherosclerotic cardiovascular disease (i.e., secondary prevention). For those younger than 40 years of age with additional cardiovascular risk, moderate-intensity statins are recommended after the healthcare provider and the patient discuss the risks and benefits of such intervention, as there is paucity of date for individuals below age 40 or above age 75 years. For those aged over 40 years without any additional risk, moderate-intensity statin is suggested in addition to lifestyle modifications, while those with any additional risk should be on high-intensity statin (i.e., primary prevention) [35]. Various statins are categorized according to their intensity in Table 40.2. The dose and

Table 40.2 Classification of statins according to their efficacy in reducing LDL cholesterol

	High intensity	Moderate intensity
Average effect on LDL cholesterol with daily dose	Lowering of LDL cholesterol ≥50%	Lowering of LDL cholesterol 30 to <50%
Examples	(a) Atorvastatin 40–80 mg (b) Rosuvastatin 20–40 mg	(a) Atorvastatin 10–20 mg (b) Fluvastatin 40 mg twice a day or extended release 80 mg once a day (c) Lovastatin 40 mg (d) Pitavastatin 2–4 mg (e) Pravastatin 40–80 mg (f) Rosuvastatin 5–10 mg (g) Simvastatin 20–40 mg

choice of statin can be adjusted based on patient's response, side effects, and tolerability. Addition of ezetimibe to moderate-intensity statin may provide additional benefits especially in patients with acute coronary syndrome and LDL cholesterol of 1.29 mmol/L (50 mg/dL) or over or for those who cannot tolerate high-intensity statin. Combination of statin and fenofibrate may be considered in men with triglyceride levels of 2.3 mmol/L (204 mg/dL) or more and HDL cholesterol level of 0.9 mmol/L (34 mg/dL) or less. Combination of statin and niacin has no benefit beyond statin therapy, may increase the risk of stroke, and generally should be avoided. Statins are contraindicated in pregnancy [35].

Lipid profile should be measured before starting statin therapy, 4–12 week after the initiation of therapy and periodically thereafter to monitor compliance and efficacy [35]. Based on the currently available literature, an evidence-based algorithm for the drug therapy of dyslipidemia in patients with diabetes is shown in Fig. 40.2. As lowering LDL cholesterol levels are irrefutably linked to reducing cardiovascular events, the first priority for most patients with CVD should be to start statin therapy irrespective of baseline lipid levels (Fig. 40.2). High-intensity statins are recommended for those with established coronary artery disease or those who have 10-year risk of ≥20%. If the LDL cholesterol response to therapy is less than 50% in a very high-risk individual, or if the patient cannot tolerate statins, then addition of ezetimibe, bempedoic acid, and PCSK9 inhibitors such as evolocumab and alirocumab should be considered especially if LDL cholesterol level is above 1.8 mmol/L (70 mg/dL) [35, 70, 71].

In general, cholesterol-binding resins are an option only if the patient's serum triglyceride concentration is less than 2.83 mmol/L (250 mg/dL) or less than 2.26 mmol/L (200 mg/dL) for those on sulfonylurea or insulin, as this class of agents might exacerbate hypertriglyceridemia. An attractive option is colesevelam as it has blood glucose-lowering effect in addition to its inhibition of cholesterol absorption [56]. In patients with established cardiovascular disease or for those with multiple cardiovascular risk factors, if triglyceride levels are 1.5–5.6 mmol/L (135–499 mg/dL), 4 g of icosapent ethyl can be added to reduce adverse cardiovascular events [65].

Currently, the principal rationale for targeting the triglyceride levels is to reduce the risk of pancreatitis. This serious complication rarely occurs when the serum triglyceride levels are less than 1000 mg/dL. However, individual variability in triglyceride-related risk should be taken into consideration when determining the threshold level below which the risk of pancreatitis is negligible.

When serum triglyceride level is over 5.65–11.3 mmol/L (500–1000 mg/dL) (the range is to account for differences in individual susceptibility to pancreatitis), fibrate with and without omega-3 fatty acids is recommended. An exception would be patients who have chylomicronemia associated with a profound lipolytic deficiency. It is noteworthy that the

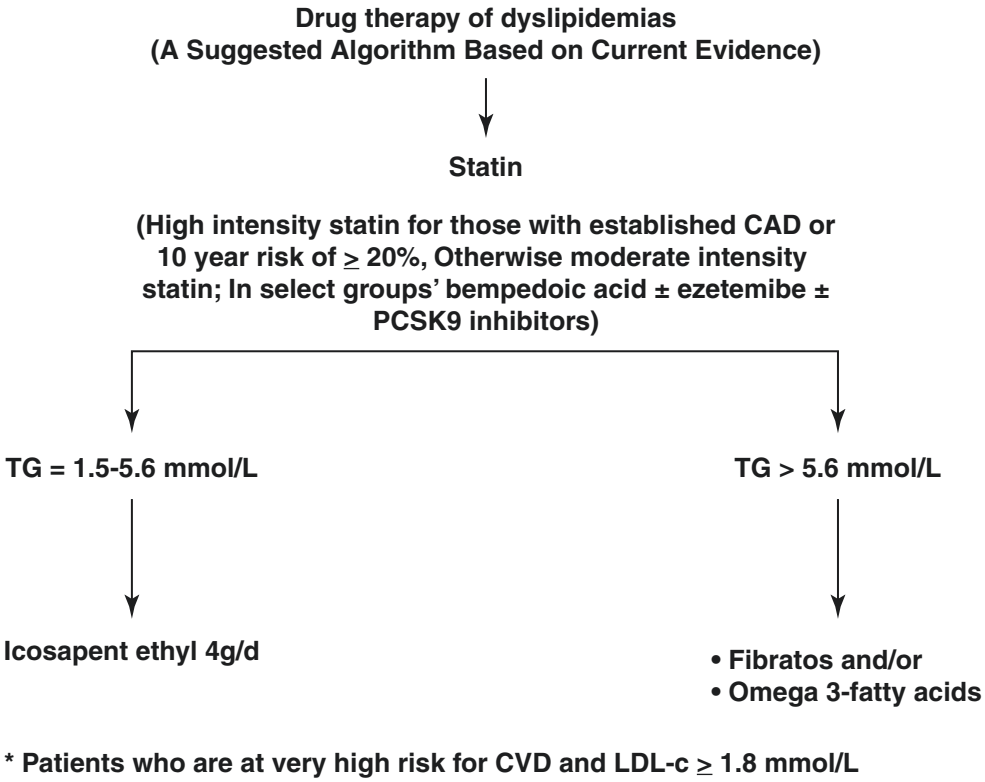

Fig. 40.2 A suggested evidence-based algorithm for drug therapy of dyslipidemia in patients with diabetes mellitus. *LDL-c* low-density lipoprotein cholesterol, *TG* triglycerides, *CVD* cardiovascular disease. Reprinted from reference [8] with some modifications and with permission of the authors and the publisher

combination of a statin and a fibrate or nicotinic acid can potentiate the risk of rhabdomyolysis, and as such, these combinations should be used cautiously.

Conclusions

Type 2 diabetes is commonly associated with atherogenic dyslipidemic profile that includes high triglycerides, low HDL, and large number of small LDL particles. Lowering LDL cholesterol with statins, ezetimibe, and PCSK9 inhibitors has proven clinical benefits. In patients with established cardiovascular disease or for those with multiple cardiovascular risk factors, LDL cholesterol goal is <1.8 mmol/L (70 mg/dL). Most patients at 40–75 years of age regardless of their basal plasma cholesterol levels require statin therapy, and high-intensity statins are recommended for high-risk patients especially those with clinically established coronary artery disease. Some individuals may benefit from combination therapy with icosapent ethyl if triglyceride levels are 1.5–5.6 mmol/L (135–499 mg/dL) [65]. Use of ezetimibe and bempedoic acid in those who cannot tolerate high-intensity statins may be prudent. In select patients, PCSK9 inhibitors are an option.

In addition to proper management of the hyperlipidemia, other risk factors frequently associated with diabetes, such as hypertension, obesity, and smoking, should be addressed.

Multiple Choice Questions

1. One of the major drivers of increased plasma triglyceride concentrations in people with type 2 diabetes is
   (a) High intake of saturated fat from animal foodstuffs
   (b) **Increased free fatty-acid release from insulin-resistant fat cells**
   (c) Inhibition of lipoprotein lipase activity
   (d) Ectopic fat distribution
   (e) All of the above
2. Diabetic dyslipidemia is characterized by
   (a) Moderate/high plasma LDL cholesterol
   (b) High plasma triglyceride levels
   (c) Low plasma HDL cholesterol levels
   (d) **All of the above**
   (e) A and B are correct
3. The increased flux of free fatty acids into the liver promotes
   (a) **Increased triglyceride, apoB, and VLDL production**
   (b) Increased total cholesterol, apo A, and LDL production
   (c) Increased triglyceride, apoA, and LDL production
   (d) Decreased triglyceride, apoB, and LDL production
   (e) Increased triglyceride, apoB, and no changes in VLDL production
4. Severe hypertriglyceridemia (greater than or equal to 5.65 mmol/L (500 mg/dL) increases the risk of
   (a) Acute myocardial infarction
   (b) Stroke
   (c) **Acute pancreatitis**
   (d) Peripheral artery disease
   (e) Acute gastritis
5. Glycemic control can be improved with:
   (a) Low carbohydrate diet
   (b) Aerobic exercise
   (c) Resistance training
   (d) Thirty minutes of walking five times a week
   (e) **All of the above**
6. Most people with diabetes would require pharmacologic agents, but lifestyle modifications are still important cornerstone of therapy when they
   (a) Include high-intensity aerobic exercise
   (b) **Achieve modest body weight loss (7%), increase physical activity and smoking cessation**
   (c) Include ketogenic diets
   (d) Increase the intake of vitamins and minerals
   (e) Are focused on dietary restrictions
7. Lowering LDL cholesterol levels is irrefutably linked to reducing cardiovascular events, the priority for most patients should be
   (a) Early insulin therapy with the goal to reduce lipolysis
   (b) **Start statin therapy irrespective of baseline lipid levels**
   (c) Additional therapy with metformin at low doses
   (d) The use of anti-platelet adhesion agents
   (e) Preparations for cardiovascular management
8. Combination therapy of statin and the following drug may increase the risk of stroke
   (a) Fenofibrate
   (b) **Nicotinic acid**
   (c) Bempedoic acid
   (d) PCSK9 inhibitors
   (e) Ezetimibe
9. In patients with established cardiovascular disease or for those with multiple cardiovascular risk factors, if triglyceride levels are 1.5–5.6 mmol/L (135–499 mg/dL)
   (a) Icosapent ethyl, 1 g/day should be added
   (b) Fenofibrate should be added
   (c) **Icosapent ethyl, 4 g/day can be added to reduce adverse cardiovascular events**
   (d) Omega-3 carboxylic acids 4 g/day can be added to reduce adverse cardiovascular events.
   (e) Recommend low carbohydrate diet
10. While statins have well established cardiovascular benefits, the following agents are also shown to be associated with reduced cardiovascular adverse events
    (a) Bempedoic acid

(b) **PCSK9 inhibitors**
(c) **Niacin**
(d) Omega-3 fatty acids
(e) Antioxidant vitamins such as vitamin E and C

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Obesity and Diabetes: Clinical Aspects

41

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Objectives

1. To contrast the utility of assessments of obesity and their accuracy in determining health risk
2. To discuss genetic, social, and environmental causes of obesity and diabetes
3. To summarize different treatment methods for obesity and diabetes

Introduction

The worldwide prevalence of obesity has been increasing since the 1980s, and by 2014, 600 million adults had obesity [1]. There are region-specific variations in these rates; nonetheless, rates of obesity have been increasing in both developing and developed nations [1]. Furthermore, it has been estimated that the rates of obesity will continue to rise and reach over 40% of adults in the United Kingdom and over 50% of adults in the United States by 2030 [2].

Obesity has been recognized as a major public health concern owing to the considerable increases in health risks associated with excess weight. Having obesity is associated with an increased risk of having chronic [3] and communicable diseases [4]. Furthermore, having obesity is associated with 4.7 to 13 years of life lost [5, 6], with the greatest decrease in life expectancy for individuals with a body mass index ≥45 kg/m^2 [5]. This places a considerable burden on healthcare systems.

It has been estimated that more than $100 billion is spent annually in the United States for direct healthcare costs associated with obesity [7, 8]. These costs can affect people both individually and systemically. For example, a study observed that patients with overweight and obesity paid considerably more (22–41%) for an emergency department visit precipitated by shortness of breath and chest pains than those with normal weight, with cost increasing per BMI category [9]. Furthermore, obesity can have considerable costs in relation to loss of productivity. Results from a large observational study in the United States observed that individuals with excess weight are 32–118% more likely to report missing work in the past year with the likelihood increasing with each BMI category [10].

Type 1 diabetes was traditionally associated with individuals with lower weight. However, with improvements in glycemic control and increasing use of insulin, a weight-promoting hormone, now many patients with type 1 diabetes also have obesity [11]. Weight management has been challenging in this group, as insulin is the primary treatment [12], and the fear of hypoglycemic can promote excessive calorie intake [13]. Type 1 diabetes and obesity are not well studied at this stage; therefore, this chapter will focus on type 2 diabetes (T2D).

Assessment of Obesity

Body Mass Index (BMI)

Body mass index (BMI) is the most commonly used method for classifying individuals as having obesity and is calculated by dividing weight in kilograms by height in meters squared. The World Health Organization (WHO) has pro-

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Table 41.1 World Health Organization's weight categories according to body mass index

Category	Body Mass Index
Normal weight	18.5–24.9 kg/m^2
Overweight	25.0–29.9 kg/m^2
Obesity class I	30.0–34.9 kg/m^2
Obesity class II	35.0–39.9 kg/m^2
Obesity class III	≥40 kg/m^2

vided guidelines for using BMI to categorize individuals as having underweight, normal weight, overweight, or obesity (Table 41.1). BMI is meant to be a measure of health, and research has suggested that increasing levels of BMI are associated with poorer health outcomes [1]. As such, obesity can be further subcategorized as: Class I: 30.0–34.9 kg/m^2, Class II: 35–39.9 kg/m^2, and Class III: ≥40 kg/m^2.

Although BMI is currently used to track trends in obesity, there are criticisms for its lack of utility in determining body composition, as well as in predicting morbidity and mortality. Additionally, due to differences in the accumulation of central adiposity, BMI thresholds may not be appropriate for all ethnicities. Indeed, a WHO expert committee [14] and other international organizations [15, 16] have recognized this issue and recommend lowering thresholds by 2.5 kg/m^2 for individuals of Asian descent. However, there is considerably variability in the health risk associated with a given BMI in all ethnic groups. For example, individuals who identify as White in the United States have a lower body fat percentage for a given BMI than those in Europe [17]. Thus, to avoid confusion and due to the lack of sufficient concise evidence, WHO guidelines still use the cutoff of a BMI ≥30 kg/m^2 for obesity [14]. Moreover, BMI does not consider a subject's body composition when classifying their health risk [18] and therefore may not be an accurate predictor of cardiovascular disease and other conditions that correlated with adipose percentage, adipose type, and location. Morbidity and mortality staging systems, such as Edmonton obesity staging system (EOSS), have been proposed for use instead of or along with BMI.

Body Circumference(s)

Waist Circumference

Excess abdominal adiposity is associated with a greater risk of death [19] and having chronic conditions such as T2D [20, 21] irrespective of BMI. As such, waist circumference can be used to assess health. However, there is considerable disagreement regarding the most optimal site to measure waist circumference. WHO recommends measuring a person's waist circumference at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest [22].

The National Institutes of Health (NIH) has identified waist circumferences ≥102 cm for men and ≥88 cm for women as an indication of increased risk of morbidity and mortality [22]. However, these thresholds have been criticized due to known ethnic differences in abdominal fat distribution [23]; therefore, ethnic-specific thresholds have been proposed to address this limitation. For example, the use of lower thresholds (87–90 cm for men, 54–77 cm for women) is recommended for South Asians as it was observed that these thresholds were more strongly associated with ill-health in this population [24]. There has also been criticism regarding the use of universal waist circumference thresholds for all BMI categories, since the NIH waist circumference thresholds were developed by taking the average waist circumference for a large sample of White men and women with a BMI of 30 kg/m^2 [25]. Therefore, the NIH thresholds may be more of a surrogate measure for BMI rather than an assessment of health risk. To address this limitation, Ardern et al. [26] developed BMI-specific waist circumference thresholds that are more strongly related to poor health. These new thresholds range from 87 cm (normal weight) to 124 cm (class II obese) in men and 79 cm (normal weight) to 115 cm (class II obese) in women.

Waist-to-Hip Ratio

Waist-to-hip ratio is another tool used to measure body fat distribution and evaluate health risks associated with excess weight [27]. Waist-to-hip ratio is calculated by dividing an individual's waist circumference by their hip circumference [18]. While there is no agreement regarding the most optimal site to measure waist circumference, in general protocols recommend that hip circumference be measured around the widest portion of the buttocks. Waist-to-hip ratios are meant to build on solely waist circumference measurements as hip circumferences are thought to provide information regarding key measures of body composition like muscle mass, while waist circumference is used to assess abdominal adiposity [28]. The WHO recommends that waist-to-hip ratios of ≥0.9 for men and ≥0.85 women be used to identify a substantially increased risk of ill-health [27].

Several criticisms regarding the utility of waist-to-hip ratio in assessing body composition and health have been made. To begin, changes in weight are not consistently correlated with changes in waist-to-hip circumferences. For example, when individuals gain or lose weight, their waist-to-hip ratio tends to increase and decrease, respectively. However, patients can have increases in their waist-to-hip ratio, while their weight remaining weight stable [29]. Research has also suggested that changes in waist-to-hip ratios independent of changes of weight are not associated with improvements in cardiovascular health risk [30]. Thus, it may be the change in weight that contributes to the changes

in waist-to-hip ratio that is associated with a risk of ill-health rather than changes in the ratio itself [31].

Body Fat

Two types of body fat are present: subcutaneous and visceral. Subcutaneous fat is located directly under the skin and is not associated with poor health [30]. On the other hand, visceral fat, also known as organ fat, surrounds the organs, and when in excess, it is closely associated with metabolic complications [32]. The total of both subcutaneous and visceral fat is considered when measuring an individual's body fat content, which is usually given as a percentage of total body mass. Many methods exist for evaluating body fat, and these methods include, but are not limited to, skinfold thickness, bioelectrical impedance analysis (BIA), dual energy X-ray absorptiometry (DEXA), and the 4-compartmental model. While there is criticism regarding the use of universal cutoffs due to ethnic differences in body composition [33, 34], cutoffs of ≥25% and ≥35% are proposed for men and women, respectively [35]. Various methods of measuring body fat are described in further detail below.

Skinfold Thickness

Skinfold thickness is measured using a caliper. The caliper is used to measure the thickness of subcutaneous adipose tissue. Measurements should be taken when an individual is standing in a relaxed position. The caliper is then used to take skinfold measurements, typically along the right side of the body, at various points such as the bicep, tricep, subscapular, and supra-iliac areas. These values are then entered into prediction equations that convert skinfold measures to body fat percentages. However, there can be considerable variability in body fat distribution based on differences in sex [36, 37], ethnicity [23], and age [37]. Thus, rather than universal thresholds, such as those recommended for BMI categorization, various population-specific equations have been suggested [38–41], such as the sex-specific equations proposed by Jackson and Pollock.

Bioelectrical Impedance Analysis (BIA)

Lean tissue is highly conductive due to its increased electrolyte and water content compared to fat, which is more of an insulator. BIA uses these differences in the flow of electric current through body tissues to estimate body fat. An electrical current is sent through your body, and based on the rate it returns, an individual's total body water can be calculated. This total body water value is then used to estimate fat free (muscle, bone, tissue) and fat mass [42].

BIA is an easy, inexpensive, and quick way to assess body fat. However, many factors can affect the accuracy of this measurement and should be controlled for when using BIA to assess body fat. Dehydration and moderate exercise increases the body's electrical resistance leading to an overestimation of body fat, and consumption of a meal decreases electrical resistance, therefore resulting in lower estimates of body fat [43]. Additionally, having excess weight is associated with greater amounts of extracellular fluids. Thus, BIA may not be an appropriate tool to assess body fat in individuals with overweight or obesity as extracellular fluids will contribute to an underestimation of body fat [43].

Dual Energy X-Ray Absorptiometry (DEXA)

DEXA was initially developed for the measurement of total bone mineral since it uses X-rays to distinguish between and measure three major bodily components: bone mineral, fat mass, and non-bone lean tissue. The advantages of using DEXA are that it operates with a safe radiation level for a whole-body scan [44] and provides a more accurate assessment of body fat than the other methods outlined above [45, 46]. However, the cost associated with the equipment and expertise to run the test often makes the use of DEXA to assess body fat prohibitive. There are also machine specifications that limit the use of DEXA for assessing body fat in individuals with severe obesity. For example, the maximum weight that most machines can hold is 300 pounds with a width of 60 cm [47]. Additionally, DEXA determines an individual's body fat based on underlying assumptions regarding the distribution of bone mineral, fat, and non-bone lean tissue, which may be inaccurate due to person-to-person variability. Similar to other tools used to assess body fat, factors such as level of hydration and age can lead to an altered body composition distribution.

The Four-Compartmental Model

To assess an individual's body fat using the four-compartment model, four measurements must be taken: (1) body weight, (2) body density, (3) total body water, and (4) total body mineral [48, 49]. Various tools can be used to measure these four factors such as water displacement tests or DEXA. Each factor is then put into a prediction equation to estimate body fat. While this method is considered more accurate than other methods for assessing body fat discussed in this chapter and is frequently used to validate more simplistic measures [49], similar to DEXA, specialized laboratory equipment costs and technician expertise mean that this method is often not practical or feasible for the rapid assessment of body fat [49].

Causes of Obesity

In the most basic terms, obesity develops as a result of an energy imbalance, in which an individual consumes a greater amount of calories than they expend. However, obesity is a complex, multifactorial disease, and there are many avenues that contribute to this energy imbalance, without one definitive cause. A system map referred to as the "spaghetti map" was constructed to describe the interplay of factors that result in the development of obesity [50]. Sixteen thematic clusters are represented on this map, which include categories such as the influence media, social, and psychological factors. Each cluster has various sub-factors, which make up this diagram, the description of which is far beyond the scope of this textbook and chapter. As such, this section will focus on the factors that are most salient to the development of obesity and T2D.

Hereditable Factors

While obesity is often viewed as a condition resulting from disordered eating or other patient choice-related cause(s), genetics play a key role in the development of obesity. Genome studies have identified over 200 genes that are associated with body weight and adiposity in mice [51]. In humans, a single-gene mutation in 11 genes was found to be responsible for the development of over 150 cases of obesity. A deficiency of the melanocortin 4 receptor (MC4) gene [52] and Prader Willi chromosomal abnormalities [53] is the most common congenital single gene mutations leading to obesity. Furthermore, genes associated with hyperphagia, a characteristic typically defined as a behavioral cause of obesity, have been identified [54]. Taken together, this evidence suggests there is likely a variety of genes and genetic mutations that have contributed to the development of obesity [51, 55].

Population studies have provided additional evidence that supports the notion of a strong hereditable component to obesity. For example, research suggests that children who have one or both parents with a BMI greater than 30 kg/m^2 are at a 2.5 to 10.4 times greater risk of having childhood obesity [56]. Moreover, studies conducted on monozygotic twins further support the influence of genes on obesity development. Studies have observed a strong correlation in the BMI of separately reared monozygotic twins ranging from 0.61 to 0.70 [57, 58]. However, this is not to discount the effects of environmental factors on the development of obesity. Indeed, when comparing the BMIs of monozygotic and dizygotic twins reared in the same environment, their BMIs were more strongly correlated than those reared apart [57].

Environmental Factors

Diet

Obesity has been referred to as over nutrition in comparison to the energy expenditure, which alludes to the importance of dietary factors in the development of this chronic disease. As energy expenditure is challenging to modify, diet frequently becomes the key modifiable risk factor. An increase in caloric consumption has been observed in most high-income countries from the 1980s through the mid-1990s that appears concomitant with increases in the prevalence of obesity [59]. There were country-specific trends in caloric consumption that further support this notion. For example, the United States had one of the largest increases in BMI over the 10-year period (1.5 kg/m^2 on average) as well as the largest increase in caloric consumption per capita (314 kcal/day). Nonetheless, researchers state that changes in absolute caloric intake alone cannot explain the increase in the rates of obesity that has been occurring over the past four decades [60]. Thus, other factors, such as the macronutrient content of an individual's diet, may also contribute to changes in weight.

The influences of individual macronutrients, such as sugar and fats, have previously been explored with equivocal results. For example, when controlling for differences in total caloric and sugar consumption, each 100 kcal increase in dietary fat has been associated with a 0.21 kg/m^2 increase in BMI [59]. Additionally, research suggests that high dietary fat intake in women with overweight or obesity who have a familial history of obesity is associated with significant increases in their BMI [61]. Conversely, a large meta-analysis observed that increased sugar intake was associated with a 0.75 kg/m^2 increase in BMI. These results are in line with the WHO recommendations to decrease the intake of free sugars to <10% of total caloric intake to decrease an individual's likelihood of having overweight or obesity and to decrease sugar intake to <5% for greater health benefits [62]. Thus, while it still remains unclear exactly how macronutrients contribute to the development of obesity, both the quantity and type of caloric intake appear to play a role.

Physical Activity

When energy expenditure is lower than caloric intake, the balance leans toward increased weight. Theoretically, increases in energy expenditure through the participation in physical activity could result in sufficient caloric deficits to delay or prevent disease onset. Indeed, increased physical activity is often associated with decreases in weight [63] and greater weight loss maintenance over the long term [64]. However, research suggests that individuals with overweight and obesity complete significantly less steps per day than their normal weight counterparts [65]. Moreover, individuals

with obesity are unlikely to meet basic public health physical activity recommendations of 30 min/day of moderate to vigorous physical activity a minimum of 5 days/week, completing only an average of 17.3 min of moderate and 3.2 min of vigorous physical activity a day.

Physical inactivity is becoming a major health concern worldwide. While individuals with overweight and obesity participate in less physical activity on average than those with normal weight, overall less than 5% of adults in the United States meet public health physical activity recommendations [65]. While purposeful physical activity, also referred to as exercise, plays a role in weight management, nonpurposeful physical activity may also be contributing to the increased rates of obesity. Indeed, adults spend more than half of their day being sedentary [65]. This is likely in part due to shifts in occupational demands during the twentieth century, which led to a decrease in physically intensive jobs, such as labor jobs, and increase in the rate of jobs with significant sedentary time, such as office managers [66]. These trends had the unintended side effect of decreasing the amount of structured nonpurposeful physical activity and therefore decreasing caloric expenditure throughout the course of a work day. Moreover, it is important to consider changes to the built environment, which has also occurred over this time period that may further contribute to physical inactivity. Research suggests that individuals who live in more walkable neighbors participate in more physical activity and are less likely to have overweight or obesity [67]. Thus, it appears that other factors, beyond personal choices, have contribute to low physical activity levels, and by extension, increase in the rates of obesity.

Type 2 Diabetes (T2D)

Obesity and a genetic predisposition are well-known risk factors for T2D [68]. The relationship between obesity and T2D is mostly described as being interdependent with obesity significantly increasing the risk of T2D, since over 90% of patients with T2D are obese [69]. Four prospective cohort studies examining the role of obesity in cardiovascular risk factors and disease concluded that children with overweight or obesity and who also had overweight or obesity as adults had increased risks of developing T2D, hypertension, dyslipidemia, and carotid-artery atherosclerosis. The risks of these outcomes among children with obesity who became nonobese by adulthood were similar to those among children who were never obese [70].

A strong association between increasing BMI and glucose intolerance exists [71]. It has been established that insulin action declines as a function of BMI. This relationship is approximately linear in both men and women, and so obesity can be considered as being in an insulin-resistant state. Moreover, a long duration of obesity is associated with lower fasting insulin levels, indicating pancreatic β-cell exhaustion. Those who had class III obesity and insulin resistance need a very large amount of insulin to maintain glucose tolerance. It is clear that individuals with obesity and insulin-resistance impose a large stress on pancreatic β-cells, and this is maintained for prolonged periods of time [71].

It must be noted that the strong associations between excess body fat and T2D do not necessarily indicate that being overweight or obese will cause T2D, since not all individuals with obesity develop diabetes and not all individuals with T2D have obesity [69]. Therefore, obesity alone is not sufficient to cause T2D. Furthermore, obesity, insulin resistance, and eventually T2D share common risk factors, as they are included in the continuum of risk factors for cardiometabolic disease. Thus, the fundamental shared risk factors for obesity and T2D at the individual level may be poor diet and physical inactivity [72]. The relationship between obesity and T2D is affected by several modifying factors, such as duration of obesity, distribution of body fat, physical activity, diet, and genetics/ethnicity [73]. In the last half century, lifestyles, including dietary habits, have changed across the world, accompanied by the global obesity epidemic. While physical activity has decreased in many regions, especially in low-income countries, in high-income countries such as the United States, overall physical activity has remained stable or even increased over the last 30 years as the obesity epidemic has mounted [72, 74]. This suggests that the main driver of the obesity epidemic in the United States may be a worsening diet, while in most low-income countries, it is likely a combination of decreased physical activity and worsening diet [72, 75, 76].

The excess adiposity accompanying T2D, particularly in a central or visceral location, is thought to be part of the pathogenic process [73]. The pathophysiological mechanism between obesity and T2D relates primarily to the adipose tissue, which has been recognized as an endocrine organ that secretes hormones and communicates with the central nervous system to regulate appetite and metabolism [73]. The increased adipocyte mass leads to increased levels of circulating free fatty acids (FFA) and other fat cell products, called adipokines. Adipocytes secrete a number of biologic products (nonesterified free fatty acids, retinol-binding protein 4, leptin, TNF-, resistin, and adiponectin). Again, studies have generally suggested that circulating levels of these products are elevated in individuals with T2D [73]. In addition to regulating body weight, appetite, and energy expenditure, adipokines also modulate insulin sensitivity. The increased production of free fatty acids and some adipokines may cause insulin resistance in skeletal muscle and liver [73] . For example, free fatty acids impair glucose utilization in skeletal muscle, promote glucose production by the liver, and impair beta cell function. In con-

trast, the production by adipocytes of adiponectin, an insulin-sensitizing peptide, is reduced in obesity, and this may contribute to hepatic insulin resistance [73]. Adipocyte products and adipokines also produce an inflammatory state and may explain why markers of inflammation such as IL-6 and C-reactive protein are often elevated in T2D [73]. Adipose tissue also can cause insulin resistance by elevating leptin levels [77]. Leptin is a protein produced by adipocytes. The main role of leptin is to regulate food intake and energy expenditure by reducing food intake and increasing sympathetic nervous system outflow, therefore inducing weight loss. Recent evidence showed that leptin levels fall during weight loss and increase brain activity in areas involved in emotional, cognitive, and sensory control of food intake [78]. Restoration of leptin levels maintains weight loss and reverses the changes in brain activity. Thus, leptin is a critical factor linking reduced energy stores to eating behavior. In obesity, the actions of both leptin and insulin within the liver are resistant. Therefore, in individuals with obesity, leptin levels are elevated, and this has been found to positively correlate with insulin resistance [78]. Leptin can impair the production of insulin and reduce the effects of insulin on the liver.

Treatment for Obesity and T2D

A modest weight loss of 5–10% has been shown to result in improvements in morbidity and mortality risks among individuals with overweight and obesity [79]. Thus, weight loss is typically prescribed to individuals with overweight and obesity. Obesity and T2D are comorbid conditions with approximately 85% of patients with T2D having overweight or obesity [69]. Moreover, excess weight has been associated with elevated blood glucose levels [80, 81]. Weight loss has been shown to result in improvements in glucose levels [82–86] and even complete remission of T2D [83, 84]. Therefore, treatments for obesity are often also prescribed for T2D. Treatment options for obesity and T2D are categorized into three domains: lifestyle, pharmacological, and surgical interventions.

Lifestyle Intervention

As with T2D, lifestyle intervention is the first-line treatment option for weight management. Lifestyle interventions for weight management consist of dietary, physical activity, or combined interventions with variable success (range: 2–13% of initial body weight loss [87, 88]). While in the short-term (<6 months), dietary and combined interventions appear to be equally more effective than those that are purely physical in nature, over the long term (≥1 year), combined interventions seem to have greater weight loss success [88–90].

The benefits of combined lifestyle interventions for glycemic control in individuals with impaired glucose tolerance (IGT) [91, 92] and T2D [93, 94] have been well established in large-scale randomized control trials. Specifically, the *Diabetes Prevention Program* (DPP) in the United States and *Finnish Diabetes Prevention study* (DPS) enrolled IGT patients and randomized them to an intensive combined lifestyle intervention program, or control, with the DPP program including a third arm prescribed metformin. Patients participating in the intensive lifestyle intervention had greater improvements in key glycemic indicators such as fasting plasma glucose [91, 92] and glycated hemoglobin [92] than controls. Moreover, a smaller proportion of patients progressed to T2D in intensive lifestyle intervention group than controls [91, 92] or those prescribed metformin [91]. In patients who already have T2D, combined lifestyle intervention can also result in significant improvements in glycemic control. The Look AHEAD study randomized patients with T2D to receive an intensive combined lifestyle intervention or a diabetes support and education group and also observed greater decreases in weight and glycated hemoglobin after 1 [93, 94] and 4 year(s) [94] of treatment in the intensive combined intervention group. Unfortunately, these improvements due to the lifestyle intervention decreased overtime [93, 94].

Currently, there is considerable disagreement regarding what is the most optimal diet, or physical activity type for weight management. For example, dietary recommendations for weight management once focused on decreasing not only caloric intake but also the intake of dietary fat as this macronutrient was thought to be associated with ill-health. However, results from several meta-analyses suggest that at 1 year there is no significant difference in the weight loss achieved by patients prescribed a low fat versus low carbohydrate diet [95–97]. When taking into consideration the management of T2D, certain types of diets may be more optimal as they are associated with not only weight loss but also improvements in glycemic control. Specifically, individuals who consumed a low carbohydrate diet had greater decreases in their glycated hemoglobin [95] than participants consuming a low fat diet.

Physical activity can be categorized as aerobic or anaerobic. Aerobic, also referred to as cardio, includes activities like running and dancing. Anaerobic, also referred to as resistance, is a type of activities that can only be performed in short bursts due to the muscle oxygen demand, such as weight lifting or sprinting. Research suggests that either aerobic or anaerobic exercise interventions can result in improvements in glycated hemoglobin; however, combined exercise interventions resulted in greater improvements than solely aerobic or anaerobic interventions [98]. Owing to the

health benefits associated with physical activity, the American College of Sports Medicine and the American Diabetes Association has released a joint statement that advocates for individuals with T2D participate in both aerobic and anaerobic physical activity weekly. Specifically, they recommend individuals with T2D participate in a minimum of 3 days/week of aerobic and 2–3 days/week of anaerobic activities for improvement in blood sugar [99]. For weight management, participating in both anaerobic and aerobic physical activity is also more beneficial than aerobic or resistance alone [100, 101]. Furthermore, a greater amount (>250 min/week vs. 150 min/week) of moderate to vigorous physical activity is recommended for significant weight loss [101].

Patients are able to achieve clinically significant improvements in their T2D and weight when implementing behavioral changes. Yet, these improvements are often transient in nature as patients are prone to regaining weight, or returning to previous habits [88, 102, 103]. This can be especially detrimental for patients with T2D as weight (re)gain is associated with a concomitant increases in glycated hemoglobin in populations with [104] and without T2D [105, 106]. Thus, the use of other interventions that can directly counteract physiological changes that make individuals prone to regaining weight, such as pharmacological or surgical interventions, may be advantageous.

Pharmacological Interventions

Pharmacological intervention is recommended for individuals who have attempted and previously failed at losing weight and have a BMI ≥30, or BMI ≥27 with at least one other medical condition [107]. Pharmaceuticals have a distinct advantage over lifestyle interventions as they directly target physiological changes that occur with and may inhibit weight loss and weight maintenance. Pharmaceutical intervention for weight can also provide additional benefits in the management of T2D beyond weight loss. Research suggest that taking weight management pharmaceuticals is associated with greater improvements in blood glucose levels and other metabolic parameters such as waist circumference and blood pressure than lifestyle intervention alone [108–110]. Moreover, patients who take weight management pharmaceuticals are also less likely to develop T2D [110], and patients with T2D have a greater rate of remission [85, 86]. Thus, effective interventions for weight management should commence as soon as T2D, or impaired glucose tolerance or abdominal obesity, is diagnosed.

Options for weight management for pharmaceuticals remain limited with only two agents available worldwide. Orlistat (Xenical), which has been available for over two decades, is the most widely approved weight management pharmaceutical. Its side effects include oily stools and fecal incontinence, which contribute to the high attrition rates (33–77% [111, 112]) observed among patients taking this agent. Patients prescribed orlistat lose significantly more weight than those just participating in lifestyle interventions, with T2D patients losing on average 4.6–6.2% of their initial body weight and significantly greater improvements in key diabetes indicators such as glycated hemoglobin and fasting blood glucose [113]. However, it is unclear whether these improvements in T2D indicators are due to the medication's effects, or to the amount of weight loss achieved.

A GLP1 analogue, liraglutide 3.0 mg (Saxenda), has been approved for use within the United States, Canada, Mexico, the United Arab Emirates, and most European countries. Several large randomized control trials, referred to as the *Satiety and Clinical Adiposity–Liraglutide Evidence in Non-Diabetic and Diabetic People* (SCALE), have examined the efficacy of this pharmaceutical for weight management. The only SCALE study that examined individuals with T2D observed that after 56 weeks of treatment, individuals taking the medication had a greater weight loss (6% vs. 2% weight loss) and improvements in glycemic control than those taking the placebo [114]. It is important to note that liraglutide 3.0 mg was initially prescribed and still remains on the market as a T2D medication (Victoza) at the maximum therapeutic dose of 1.8 mg, which may allude to greater beneficial effects in respective to the management of T2D compared to other weight management pharmaceuticals. Only one study has directly compared the efficacy of orlistat, liraglutide, and lifestyle modification for weight management, but it excluded individuals with T2D [109]. Nevertheless, patients in this study who were prescribed liraglutide 3.0 mg lost more weight and had greater improvements in their blood glucose than patients prescribed orlistat or just a lifestyle intervention after 20 and 56 weeks of treatment [109].

Other pharmaceuticals available for weight management include a phentermine and topiramate combination (Qsymia), a bupropion and naltrexone combination (Contrave), and lorcaserin (Belviq). However, these pharmaceuticals are only approved for weight management in the United States and are under review in Canada, Europe, and other countries. Several studies have examined the efficacy of these medications for glycemic control and weight management in individuals with T2D. All three of these medications resulted in significantly greater weight loss (lorcaserin: −9.3 vs. −7.5 kg [82], phentermine/topiramate: −9.1 vs. −2.6 kg [85], and bupropion/naltrexone: −5.3 vs. −1.9 kg [86]) than placebo. Moreover, patients with T2D had greater improvements in their glycated hemoglobin and required the addition of less T2D medication to control their blood sugars than those just participating in the lifestyle intervention [82, 85, 86].

The prescription of pharmaceuticals is much more common in the treatment of T2D than weight. This may be due

to the more acute detrimental effects that high blood glucose can have on a patient when the effects of excessive weight tend to occur over the long term. Diabetes medications can have a beneficial (i.e., metformin, liraglutide) or detrimental (i.e., insulin, secretagogues) effect on a patient's ability to lose weight [107, 115, 116]. Thus, it is important to consider the effects that these medications can have on a patient's weight prior to prescribing them. This is in line with recommendations from The Endocrine Society, which recommended weight-losing and weight-neutral medications as first- and second-line agents for T2D management in patients with overweight or obesity [107]. Further, if insulin therapy is necessary, it is recommended to co-prescribed a diabetes medication with weight negative properties to mitigate the weight gain typically associated with insulin [107]. Given the association between weight gain and elevated blood glucose levels [80, 81], it may be advantageous to prescribe weight neutral and weight negative T2D medications as first- and second-line treatment of diabetes in lean populations as well as overweight and obese.

Surgical Intervention

Compared to lifestyle and pharmaceutical interventions, patients who undergo bariatric surgery lose more weight and maintain a greater proportion of this loss over the long term, making bariatric surgery the most effective treatment for obesity [117]. However, there are lifelong dietary changes and potential complications that accompany this intervention [117–119], which had meant that until recently, bariatric surgery was reserved for individuals with severe obesity. Multiple international organizations [15, 16] recommend bariatric surgery for individuals who had previously failed at weight loss and have a BMI $\geq$40 kg/m^2 or a BMI $\geq$35 kg/m^2 with at least one comorbidity. However, with bariatric surgery being recognized as a metabolic surgery due to the reduction in cardiometabolic risk factor levels observed post-surgery, as well as due to the differences for disease risk attributed to excess weight by ethnicity, these organizations now recommend consideration of patients with lower (i.e., <35 kg/m^2) BMIs for this surgery.

The International Federation for the Surgery of Obesity and Metabolic Disorders surveyed national organizations in 56 countries to determine trends in bariatric surgery. This survey contained 16 possible procedures. Sleeve gastrectomy was the most common procedure (45.9%), followed by roux-en-y gastric bypass (39.6%), and then gastric banding (7.4%), with no other procedure accounting for greater than 2% of procedures performed worldwide [120]. Below is a brief description of the three most common surgical procedures:

- Roux-En-Y gastric bypass: A small portion of the upper stomach is made into a pouch and is attached to the jejunum, bypassing a portion of the digestive system and making a y shape, which gives this procedure its name [117]. This procedure is referred to as both a restrictive and malabsportive weight loss procedure. It is considered restrictive as the resizing of the stomach restricts the amount of food that a patient can consume and malabsorptive, as bypassing part of the stomach and intestine results in decreased absorption of nutrients.
- Sleeve gastrectomy: A large portion of the stomach is removed, and the remainder is stapled closed resulting in a smaller tubular shaped stomach [119]. This is a purely restrictive as the new smaller size of the stomach decreases the amount of calories the patient can consume [121], but no bypassing of the digestive system takes place to result in malabsoprtion.
- Gastric banding: A small, thin band, typically made of a flexible material such as silicon, is placed around the upper stomach to create a pouch [117]. Similar to the sleeve gastrectomy, this is a purely restrictive procedure. For the majority of patients, frequent adjustments to the band are necessary within the first 2 years to promote and maintain weight loss [122].

Bariatric surgery is a relatively safe procedure, with 30-day mortality rates ranging from 0.05% to 0.5% [119, 123] and 30-day complication rates of 1.4–5.9% [119]. One-year post-surgery, patients who underwent sleeve gastrectomy (range: 68.2–69.7% excess weight [123, 124]) and roux-en-y (60.5–62.6% excess weight [118, 123, 124] appear to lose comparable amounts of weight, and patients who underwent gastric banding (42.6–47.5% excess weight [118, 123]) have considerably less weight loss.

Bariatric surgery may be one of the best tools for the management and treatment of T2D. Patients with T2D typically lose less weight than nondiabetic populations in lifestyle and pharmaceutical interventions. However, a meta-analysis observed that patients in the T2D sub-sample lost more weight than the full sample of patients with and without T2D. This may suggest the lower mean weight loss in the full sample was due to less optimal weight outcomes in patients without T2D [84]. Moreover 86.6% of patients with T2D experience improved or complete resolution of their diabetes post-surgery [84]. Over half of patients with T2D that undergo bariatric surgery have complete resolution of their diabetes regardless of the procedure; however, the proportion of patients who go into remission is significantly greater for those with sleeve gastrectomy (79.7%) and roux-en-y (80.3%) than those with gastric banding (56.7%) [84]. Lastly, patients who undergo bariatric surgery can have additional benefits beyond significant weight loss and improvements or resolution of their T2D or IGT, such as

a decrease in mortality risk [125–127] and risk of T2D complications [126, 127].

Gastric banding is now being recognized as an inferior bariatric surgery procedure, likely due to the decreased weight loss and improvements in comorbidities. Furthermore, due to complications and insufficient weight loss, over half of patients who undergo gastric banding will need band removal and conversion to another type of bariatric procedure [128]. Owing to these suboptimal outcomes, the Canadian Diabetes Association has recommended against the use of the gastric band [12]. This may mean that other procedures will increase in popularity as gastric banding falls into disuse. For example, a less common surgery that is gaining traction is the bilio-pancreatic diversion with the duodenal switch. This procedure is more invasive than the other three procedures discussed but has better results in terms of diabetes remission and long-term weight loss than the more common alternatives (i.e., roux-en-y bypass and gastric banding) [84].

Conclusion

Obesity is a chronic disease categorized by excessive weight with ill-health effects. BMI is the most common tool to categorize obesity, with a recommended threshold of ≥30 kg/m^2. There are many different methods to assess obesity; however, due to considerable differences in the associations of excess weight and ill-health based on age, sex, and ethnicity, heavy criticism exists regarding the use of universal thresholds. Nonetheless, these measurements remain in use due to their ability to assess the potential health impacts of excess weight.

Obesity is a chronic, multifactorial disease. Multiple factors have been identified that are associated with developing obesity, with genetics, diet, and physical activity being the factors that are most salient to obesity and T2D. Mechanistic studies have determined the presence of several genes associated with having obesity, and epidemiological studies have further supported this evidence. Increased caloric intake, macronutrient content, and lack of physical activity also play a role in the development of obesity, but these are modifiable risk factors, which can be manipulated in the treatment of these conditions.

Treatment options for obesity, as with T2D, can be categorized as lifestyle,

Pharmacological, or surgical. Lifestyle intervention is a first line of treatment; however, treatment benefits are often not maintained over the long term. Thus, medications and surgery provide additional opportunities for weight management and have been shown to have greater efficacy for weight loss and improvements in comorbidities than lifestyle interventions alone.

Concluding Remarks

1. Obesity is a chronic medical characterized by excess weight associated with ill-health effects. For trend analysis and owing to the ease of measurement, a BMI ≥ 30 kg/m^2 is the most frequently used definition.
2. A multitude of factors contribute to the development of obesity; however, genetics, diet, and physical activity are the most important. T2D is closely linked to obesity and share similar biological processes and epidemiology.
3. Lifestyle, pharmaceutical, and surgical treatment options all have the potential to improve and eliminate the negative health effects of T2D or excess weight; however, surgical interventions are the most successful.

Multiple Choice Questions

1. Body mass index is a tool commonly used to classify an individual as having obesity. What threshold is used to define obesity?
   (a) Greater than or equal to 27.5 kg/m^2
   (b) **Greater than or equal to 30 kg/m^2**
   Although there is variability in the ill-health effects associated with a given BMI based on ethnicity, the World Health Organization still recommends a threshold of 30 kg/m^2 to define obesity.
   (c) Greater than or equal to 35 kg/m^2
   (d) Greater than or equal to 40 kg/m^2
   (e) No threshold exists
2. Which of the following are methods used to assess obesity?
   (a) Skinfold measures
   (b) Dual Energy X-ray Absorptiometry (DEXA)
   (c) Forehead circumference
   (d) **A & B**
   Many circumference measurements are used to assess obesity such as waist, hip, and neck circumferences, but forehead circumference is not one of them.
   (e) All of the above
3. What are some common demographics that make the use of absolute thresholds for the assessment of obesity and its ill-health effects difficult?
   (a) Age
   (b) Sex
   (c) Ethnicity
   (d) **All of the above**
   Age, sex, and ethnicity can all change the association that excess weight can have with ill-health.

For example, some excess weight may actually be beneficial to elderly populations as it has been shown to decrease frailty. Women are able to have higher body fat percentages than men without ill-health effects. Furthermore, certain ethnicities, for example, people of Asian descent, start to have exhibit ill-health effects at lower levels of body fat than White counterparts.

(e) None of the above

4. Which of the following is true regarding the notion that there is hereditary component to the development of obesity?
   (a) Children who have one parent with obesity are at a greater risk for developing obesity than those with two
   (b) BMIs of monozygotic and dizygotic twins raised together are more similar than those raised apart
   (c) Genes have been found that are associated with hypophagia
   (d) All of the above
   (e) **None of the above**

   Children who have two parents with obesity are at a greater risk of having obesity, and genes have been identified associated with hyperphagia (excessive eating). Furthermore, while it is true that the BMI of twins reared together are more similar than those raised apart, there is still a strong association in the BMIs of twins reared apart.
5. Which of the following are patient modifiable risk factors associated with the development of obesity?
   (a) **Physical activity**

   Physical activity is the only factor that listed that individuals have control over. While it is possible for the built environment to be modified to encourage more physical activity, this is not something that an individual would be able to change by themselves.

   (b) The built environment
   (c) Genetics
   (d) Type 2 diabetes
   (e) A & B
6. Which of the following diet and physical activity factors contribute to the development of obesity?
   (a) Excessive caloric intake
   (b) Being sedentary
   (c) Macronutrient content of diet
   (d) Employment
   (e) **All of the above**

   Beyond the typical modifiable factors that are addressed in the treatment of obesity, such as diet and physical activity, other factors, such as your employment, can contribute to weight gain. This is due to occupational shifts that have occurred during the twentieth century that have resulted in an increase in management and decrease in labor type jobs.
7. Adipokines secreted by adipocytes, regulate body weight, appetite, and energy expenditure. They also contribute to increasing insulin resistance by?
   (a) Increasing lipid production
   (b) Decreasing leptin levels
   (c) **Modulating insulin sensitivity**

   In addition to regulating body weight, appetite, and energy expenditure, adipokines also modulate insulin sensitivity. The increased production of free fatty acids and some adipokines may cause insulin resistance in skeletal muscle and liver.

   (d) Promoting beta cell function
   (e) Reducing markers of inflammation
8. Which of the following statements is true regarding low fat and low carbohydrate diets?
   (a) Low fat diets are more beneficial for weight loss, but low fat and low carbohydrate diets are equally effective for managing diabetes management.
   (b) Low carbohydrate diets are more beneficial for weight loss, but low fat and low carbohydrate diets are equally effective for diabetes management.
   (c) Low fat and low carbohydrates are equally beneficial for weight loss, but low fat diets are more beneficial for diabetes management.
   (d) **Low fat and low carbohydrates are equally beneficial for weight loss, but low carbohydrate diets are more beneficial for diabetes management**.

   While low fat and low carbohydrates do appear to be equally effective for weight management, diets low in carbohydrates appears to be more beneficial for patients with T2D. Indeed, research has suggested that T2D consuming diets lower in carbohydrates will have greater improvements in glycemic control than consuming a low fat diet.

   (e) Low fat and low carbohydrate diets are equally effective in the management of obesity and diabetes.
9. Which of the following statements is false regarding weight management medications:
   (a) **Weight management medications decrease weight, but do not provide any benefits for the management of diabetes**

   Each of the available weight management medications have been tested in populations with T2D, and all have been shown to improvement glycemic control. Furthermore, these patients typically require the addition of less glycemic medication than those given a placebo.

   (b) Liraglutide 3.0 mg is more effective for glycemic control than orlistat.

(c) All approved weight management medications are associated with greater improvements in glycated hemoglobin than lifestyle intervention alone.
(d) Patients prescribed weight management medications lose significantly more weight than those participating in only lifestyle interventions.
(e) Liraglutide, a weight management medication, is also available as a T2D medication at a lower therapeutic dose.

10. Which of the following correctly lists the three treatment options for obesity and T2D in order from most to least effective?
(a) Medication, lifestyle, and surgical
(b) Lifestyle, medication, and surgical
(c) **Surgical, medication, lifestyle**
Patients who undergo surgical intervention lose more weight and have greater rates in T2D remission than patients taking weight management medications or just lifestyle intervention. Furthermore, patients taking weight management medications have greater improvements than lifestyle alone.
(d) Surgical, lifestyle, medication
(e) They are all equally effective treatments for weight and diabetes management.

Glossary

Bariatric Surgery It is a type of surgical procedure that decreases the amount of calories a patient can consume and/or digests to result in significant weight loss. Types of bariatric surgery include roux-en-y gastric bypass, sleeve gastrectomy, and gastric banding.

Body Fat It is the amount of subcutaneous and visceral fat in a person's body that can be presented as an absolute value or percentage.

Body Mass Index It is the most common tool to assess obesity. It is calculated by dividing weight in kilograms by height in meters squared.

Malabsorptive Bariatric Surgery It is a bariatric surgery procedure that alters a patient's digestive tract to decrease the amount of nutrients they can absorb from calories consumed. Examples of types of bariatric surgery that use this technique include the roux-en-y gastric bypass and bilio-pancreatic diversion with the duodenal switch.

Metabolic Surgery It is a newer term used to refer to bariatric surgery owing to the drastic improvements in metabolic conditions that have been observed post-surgery.

Obesity It is excess body weight associated with ill-health. Multiple objective methods exist to classify obesity, with a BMI greater than or equal to 30 kg/m^2 the most common.

Restrictive Bariatric Surgery It is a bariatric surgery procedure that decreases the amount of calories a patient can consume by decreasing the size of the stomach. Examples of types of bariatric surgery that use this technique include the sleeve gastrectomy and gastric banding.

Subcutaneous Fat It is the type of body fat located just beneath the skin and can be felt by pinching the skin.

Visceral Fat It is the type of body fat located internally around the organs. As such, visceral fat is also called organ fat.

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Metabolic and Bariatric Surgery in Diabetes Management

42

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Objectives

1. To describe the types and principles of the distinct bariatric surgical techniques
2. To define the clinical outcomes of most performed bariatric procedures
3. To illustrate the molecular and other mechanisms that explain metabolic outcomes of bariatric surgery
4. To explain the evolving bariatric techniques

Introduction

Bariatric surgery is the conjunct of surgical techniques to induce weight loss and metabolic health in morbidly obese patients. The recommendations for bariatric surgery are BMI ≥ 40 kg/m^2 or BMI 35–39.9 kg/m^2 with at least one comorbidity associated to obesity or clinical condition with impaired quality of life [1] (Table 42.1).

Bariatric surgery is currently the most effective treatment for severe obesity. Its effects are defined according to the amount of weight loss (surgery success has been defined as ≥50% excess weight loss [2]), mortality, quality of life, and social function, which are all positively modified as observed in several studies [3].

Bariatric surgery first evolved from a bowel resection [4], and the first Roux-en-Y gastric bypass (RYGB) [5] was intended for the treatment of obesity [4, 5]. Since then, numerous techniques have been introduced, and technology has migrated the open-surgery approach to the endoscopic, laparoscopic, and robotic approaches. Such minimally invasive methodologies and the enhanced recovery aim after bariatric surgery have significantly reduced risks and complications driven by the surgery.

Throughout time, metabolic improvements after bariatric surgery were responsible for shifting bariatric surgery to metabolic surgery, a concept first proposed by Buchwald and Varco in 1978 [6, 7]. For instance, type 2 diabetes (T2D) and other various metabolic abnormalities were resolved or remitted shortly after surgery. Metabolic surgery has been proved by randomized controlled trials to be safe and a more effective treatment for obesity and T2D compared with conventional medical multidisciplinary approach (lifestyle changes or pharmacotherapy) [8–10].

In fact, metabolic surgery could be considered in obesity class 1 (BMI 30–34.9 kg/m^2) and diabetic subjects when hyperglycemia is inadequately controlled despite medical treatment [11]. Thus, since 2016, the American Diabetes Association (ADA) includes metabolic/bariatric surgery in their Standards of Care for Diabetes algorithm [12].

Different recommendations in this regard are still valid, and consensus should be gained in years to come. Finally, bariatric surgery and its metabolic effects represent, to date, the most effectual tool for obesity treatment. Importantly, the investigation of the mechanisms associated with massive weight loss and metabolic improvements will enlighten the medical community toward the understanding of processes involved in the development of obesity and related diseases.

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Table 42.1 Obesity-related comorbidities to indicate bariatric surgery in patients with a BMI of 35–39.9 kg/m^2

T2D	Obesity-hypoventilation syndrome
High risk of T2D-insulin resistance, prediabetes, and/or metabolic syndrome	Pickwickian syndrome
Nonalcoholic fatty liver disease (NALFD)	Idiopathic intracranial hypertension
Nonalcoholic steatohepatitis (NASH)	Gastroesophageal reflux disease (GERD)
Obstructive sleep apnea (OSA)	Severe venous stasis disease
Osteoarthritis (knee/hip)	Impaired motility due to obesity
Urinary stress incontinence	Considerably impaired quality of life

Types of Bariatric Surgery

Traditionally, bariatric procedures have been characterized as restrictive [laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy (SG)]; malabsorptive [biliopancreatic diversion with duodenal switch (BPD-DS), single anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S)]; and mixed procedures [Roux-en-Y gastric bypass (RYGB)] [1]. However, now we know that not only energy restriction and nutrient absorption explain profound weight loss, but other mechanisms are involved. Here, we describe the most common techniques and their mechanisms of action as well as their influence on improved metabolism.

Laparoscopic Adjustable Gastric Band (LAGB)

In this procedure, a silicone band is placed around the gastric cardias, creating a small gastric pouch (approximately 30 mL) and restricting food intake. The band is connected to a port that is fixed at the abdominal wall [13]. Through this port, sterile saline is injected to adjust the inner diameter of the band. The reduction of this diameter decreases the gastric pouch emptying and consequent food intake. The adjustment of the band can be changed over time depending on the evolution of the patient (Fig. 42.1a).

Sleeve Gastrectomy (SG)

SG was initially performed as the first step of the laparoscopic biliopancreatic diversion to reduce the high morbidity in super-obese and/or high-risk patients [14]. Because of adequate weight loss in this group of patients, SG was accepted in 2012 by the American Society for Metabolic and Bariatric Surgery (ASMBS) as an independent bariatric procedure [15]. SG is currently the most common procedure performed in the United States [16] and worldwide [17, 18]. The latter is because while it offers adequate success rates, it is also a less technically challenging procedure, representing lower morbidity and mortality compared with the RYGB [19].

The SG technique consists of the dissection of the greater curvature of the stomach. This is performed from 2 to 6 cm proximal to the pylorus toward the angle of His. Then, an orogastric bougie (32–36 Fr) is placed and used as a guide for vertical gastric transection. Approximately 80% of the body and gastric fundus is resected and removed, leaving a tubular pouch or sleeve-shaped stomach [19, 20] (Fig. 42.1b).

Roux-en-Y Gastric Bypass (RYGB)

Currently, RYGB is considered the "gold-standard" weight loss surgery and was, until recent years, the most frequently performed bariatric surgery [17]. The procedure has several components: gastric remnant, gastric pouch, gastrojejunal and jejunojejunal anastomosis, alimentary limb, biliopancreatic limb, and common limb. A small gastric pouch (30–50 mL) is constructed by dividing the gastric cardias from the rest of the stomach. Then, the jejunum is divided 40–150 cm distally to the ligament of Treitz, creating two limbs. The proximal limb is called biliopancreatic limb (BPL) (from the excluded stomach to the proximal division of the jejunum) and distal limb, which will be connected to the gastric pouch (gastrojejunal anastomosis). The biliopancreatic limb is anastomosed to the jejunum (from 75 to 150 cm distally to the gastrojejunal anastomosis). This anastomosis will divide the distal limb into alimentary limb (from GJA to JJA) and common limb. The distal intestine is called common limb (from JJA to terminal ileum) [21] (Fig. 42.1c).

Biliopancreatic Diversion with Duodenal Switch (BPD-DS)

BPD-DS is the most effective surgical treatment for severe obesity and T2D [8, 22]. Nevertheless, because it is a technically challenging surgery with the highest postoperative complication rate, this is the most infrequent procedure [23]. The technique consists of two stages, which may be performed in one or two surgeries depending on the presence of super-obesity and, thus, the patients' risk. During the first stage, an SG is performed. In the second stage, the duodenum is transected, and its proximal part is anastomosed at 250 cm proximal to the ileocecal valve (alimentary limb). The excluded limb (biliopancreatic limb) is connected, creating an ileal-ileal anasto-

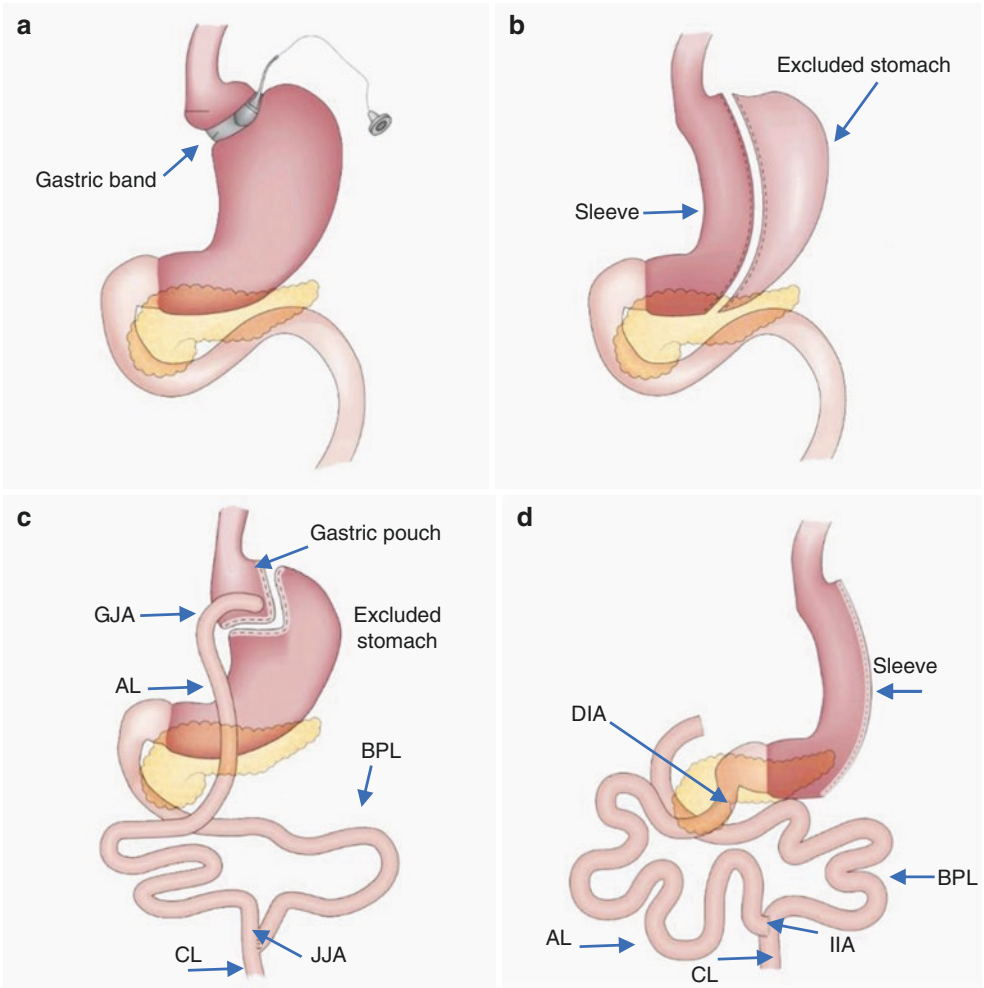

Fig. 42.1 (**a**) Laparoscopic adjustable gastric band (LAGB). (**b**) Sleeve gastrectomy (SG). (**c**) Roux-en-Y gastric bypass (RYGB). (**d**) Biliopancreatic diversion with duodenal switch (BPD-DS). *GJA* gastrojejunal anastomosis, *JJA* jejunojejunal anastomosis, *AL* alimentary limb, *BPL* biliopancreatic limb, *CL* common limb, *DIA* duodeno-ileal anastomosis, *IIA* ileoileal anastomosis

mosis, 100 cm proximal to the ileocecal valve, generating a common limb in a *Roux-en-Y* configuration. The main difference between a BPD-DS and an RYGB is the length of the small intestine bypassed, which, in the case of BPD-DS, is substantially greater than RYGB, resulting in increased malabsorption of nutrients (Fig. 42.1d).

One Anastomosis Gastric Bypass (OAGB)

OAGB, initially named mini-gastric bypass, was introduced in 2001 by Rutledge et al. as a simple and effective treatment for morbid obesity [24]. In 2005, Carbajo et al. proposed a modification of this technique and changed the name to one anastomosis gastric bypass [25]. There is currently an increasing number of OAGB performed worldwide [26–29]. OAGB is not yet accepted as a treatment for morbid obesity in the United States due to a lack of prospective and long-term follow-up studies [29].

The OAGB technique begins with the construction of a long sleeve-like gastric pouch using a 36 Fr bougie as a guide. Then, this gastric pouch is anastomosed to the jejunum (from 200 to 300 cm distally to the ligament of Treitz) in a Billroth II-like style [30, 31].

Single Anastomosis Duodeno-ileal Bypass with Sleeve Gastrectomy (SADI-S)

SADI-S is a relatively new surgical technique, introduced in 2007 by Sanchez Pernaute et al., described as a modification of BPD-DS in an effort to simplify the technique and reduce the complications associated to a long anesthetic procedure [32]. In 2020, the ASMBS accepted the SADI-S technique as an appropriate metabolic bariatric surgery [24].

The SADI-S technique comprises two stages. First, a tubular gastric pouch is created, wider than an SG, using a 54 Fr bougie. Second, the duodenum is sectioned, and its distal part is anastomosed with the ileum (200–300 cm proximal to the ileocecal valve). This Billroth II-like configuration in comparison to the *Roux-en-Y* decreases by half the number of anastomosis and has no mesentery opening, reducing operative time and the risk of intestinal obstruction [32].

Mechanisms of Action of Bariatric Surgery

Despite the effectiveness of bariatric surgery for the treatment of morbid obesity and associated metabolic diseases [9, 33, 34], its underlying mechanisms of action remain unclear. Several mechanisms have been related to bariatric/metabolic surgery, from food intake restriction and malabsorption, hormone release, and gut microbiota composition modifications, all of which influence metabolism.

Gastric Volume Restriction

Over the years different gastric restriction techniques have been performed, varying from 15 to 200 mL gastric capacity; nevertheless, no correlation has been found between stomach volume and weight loss [35]. Other mechanisms like gastric emptying speed, increase of intragastric pressure, as well as changes in gastrointestinal hormones may be involved in weight loss in the gastric restrictive bariatric procedures.

Malabsorption

The malabsorption of nutrients is achieved after bypassing distinct lengths of the small intestine. In 2010, Odstrcil et al. reported that malabsorption accounted for approximately 6% and 11% of the total reduction in combustible energy absorption at 5 and 14 months after RYGB, secondary to fat malabsorption with little or no malabsorption of proteins and carbohydrates [36].

Enteroendocrine Modifications

Since several hormones that control appetite and satiety processes are derived from the gastrointestinal tract, and bariatric surgery modifies the size and capacity of the stomach and/or the gut, then metabolic changes driven by the surgery have been found associated with altered pancreatic and gut peptide profiles [37]. Here, we will review the peptides that have been investigated and related to the metabolic outcomes of bariatric surgery.

Ghrelin

Ghrelin is secreted by the gastric and duodenal enteroendocrine cells and is not fully activated until acetylated. Once acetylated due to the action of ghrelin-O-acyltransferase (GOAT), it exerts an orexigenic action at the central nervous system (CNS), increasing food intake. In fasting conditions, ghrelin is acetylated, which is able to activate the growth hormone secretagogue receptor (GHSR) found in the hypothalamus and pituitary glands [38]. During obesity, the acetylated levels of ghrelin are apparently higher compared to those levels of ghrelin in lean subjects [39].

After bariatric surgery, mixed results regarding the circulating levels of ghrelin have been found, depending on the surgical technique. While gastric banding has been associated with increased ghrelin concentrations [40], RYGB and SG have been related to decreased levels of the hormone [41–43]. This could be attributed to the fact that RYGB excludes the gastric fundus, reducing the contact between ghrelin-producing cells and ingested food. However, further research is needed to elucidate the involvement of ghrelin in the short- and long-term effects of bariatric and metabolic surgery.

Incretins

Interestingly, weight loss or regain following combined restrictive-malabsorptive bariatric surgery is not predictive of diabetes remission, and glycemic control has been observed to improve soon after surgery, before clinically significant weight loss [44–47]. Due to the timing of these observations following surgery, other mechanisms related to the anatomical reconstruction of the GI tract are likely present to account for this. One explanation for such rapid responses relies on the variable concentrations of incretins after surgery.

Incretins are intestinal peptides known for stimulating insulin production after food intake. The main incretins are GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1), which are specifically secreted from K cells in the small intestine and L cells in the ileum and colon, respectively [48]. Some clinical reports have described reduced fasting and postprandial concentrations of GIP after bariatric surgery [49, 50]. However, other groups have not found the same, and it is possible that these controversies rely on the type of procedure and diabetes diagnosis before surgery [51–53].

On the other hand, GLP-1 has shown, more consistently, that its concentrations are modified shortly after bariatric surgery and that this peptide represents a possible and partial explanation for some metabolic consequences of the surgery. Although using a small cohort, a prospective study found that total GLP-1 levels and the incretin effect were dramatically increased within 1 month of RYGB surgery and prior to clinically significant weight loss [52].

Indeed, analogs of GLP-1 (i.e., liraglutide, semaglutide) have been used for the treatment of both obesity and diabetes, establishing weight loss reductions of 5–10% and improved glucose tolerance in patients with T2D [54]. Acute and marked increases of circulating GLP-1 after LAGB, RYGB, and SG have been reported by several [55–57], and such increases are not achieved by patients that lose similar amounts of weight due to energy restriction [52]. Furthermore, it has also been suggested that higher serum concentrations of GLP-1 are associated with better weight loss results 1 year after the surgery [42].

Mechanisms that possibly explain rises in GLP-1 after surgery highlight the “hindgut hypothesis” versus the “foregut hypothesis [58, 59]. The former states that improved glucose homeostasis is caused by the delivery of nutrients to the

distal part of the small intestine to enhance the secretion of factors involved in glucose metabolism, and the latter adjudicates the lower glucose concentrations to the exclusion of the duodenum and jejunum from their interaction with nutrients. The main candidate molecule supporting the hindgut hypothesis is GLP-1, which exerts its effects via several pathways. First, the peptide decreases appetite and gastrointestinal motility in humans, reducing food consumption [60]. Also, the insulinotropic properties of GLP-1 are associated with increased insulin gene transcription and biosynthesis, as well as increased *glucokinase* and *Glut2* gene expression [61, 62]. Finally, GLP-1 has been associated with increased beta cell proliferation and decreased apoptosis [63].

Although the effects of GLP-1 account for some of the observed consequences of bariatric surgery, additional mechanisms are involved. For instance, humans using the specific GLP-1 receptor antagonist exendin 9-39 and animal models that lack GLP-1 receptor expression and, thus, have GLP-1 ablated response show similar weight loss after RYGB and SG [64], evidencing the influence of other factors in the process.

Other gut hormones that have been found implicated in the metabolic changes after bariatric surgery are cholecystokinin (CCK), pancreatic peptide YY (PYY), pancreatic polypeptide (PP), and secretin, among others. CCK is a hunger suppressant and a stimulator of digestion, which apparently increases after SG more than after RYGB [65, 66]. PYY delays gastric emptying, alters colon motility, and regulates appetite centrally [67–69]. Seemingly, PYY increases postprandially after bariatric surgery independent of the type of procedure [55]. Despite the extensive research and recent findings, further research is needed to better understand the role of these gut hormones in bariatric surgery.

Adipokines

Several adipokines (molecules that are released from adipose tissue) have been explored regarding their concentrations and influence over metabolic surgery. The most well-known adipokines are leptin and adiponectin. Leptin represents the communicator between adipose tissue and the CNS to suppress food intake during energy sufficiency [70]. During obesity conditions, resistance to the action of leptin concurs with hyperleptinemia. Adiponectin acts on peripheral tissues, exerts anti-inflammatory and insulin-sensitizing actions, and is decreased in serum of obese subjects [71]. In fact, the secretion of this adipokine is considered to be a hallmark of healthy adipocyte function [72]. After bariatric surgery, leptin decreases and adiponectin increases, which suggests gain of adequate function of the adipose tissue [73–77]. Interestingly, some groups found that adiponectin production was significantly increased 2 weeks after the surgery when weight loss has not occurred yet, meaning that adipokine promotion is independent of massive weight loss [78]. Along with adipokine secretion modifications, adipocyte size and adipose tissue structure have also been reported different after surgery [79]. The surgery-derived modifications in adipose tissue could be contributing to decreased chronic inflammation, which is thought to be one of the most important mediators of metabolic improvement after surgery. However, the global contribution of adipose tissue and derived hormones on metabolic improvements mediated by bariatric surgery needs to be revealed yet.

Gut Microbiota

The human intestinal tract contains an extraordinary conjunct of microorganisms, namely, the bacterial component of the human gut microbiota. The number of genes in the human gut microbiota exceeds the human genome by 150-fold [80], and it confers metabolic advantages such as vitamin and fatty acid generation, carbohydrate fermentation, and bile acid metabolism.

It has been shown that in addition to weight loss and glucose tolerance, RYGB modifies gut microbiota composition and diversity within 3 months and later, during a long-term period [81]. Compared with controls, and at the phylum level, RYGB increased the abundance of Proteobacteria and Bacteroidetes and decreased Firmicutes [82–84].

Although SG has also been related to microbiota modifications, RYGB has more robust effect on the composition of gut microbiota. One possible reason for this difference is that compared with RYGB, SG induces relatively mild physical manipulations of the intestinal tract. Additionally, with exposure of the luminal contents of the intestine to an aerobic environment during prolonged surgery or increased concentrations of swallowed air reaching the gut with RYGB compared to SG, the survival of obligate anaerobic bacteria is threatened, and it may contribute to the expansion of aerobic bacteria populations in the gut microbiota following bariatric/metabolic surgery.

Bile Acids

Bile acids play a role in glucose and lipid homeostasis. The bile acid receptor FXR not only regulates bile acid synthesis but also stimulates glycogen synthesis, decreases gluconeogenesis, and increases glycolysis [85]. Bile acid receptor TGR5 activation has been associated with gallbladder filling, modulation of energy expenditure, GLP-1 release from L cells, reduction of inflammatory mediators, and suppression of hepatic glycogenolysis [72, 86–89]. Multiple studies have reported increased fasting and postprandial bile acid concentrations following RYGB [90–92]. The mechanisms involved have not been identified. Several physiologic processes altered by metabolic surgery are associated to elevated concentrations of bile acids. Whether these processes are modified by the change in bile acid concentrations remains unclear.

Histological and Anatomical Changes

Alterations in pancreatic and hepatic tissue and blood flow can be seen after bariatric surgery. Immonen et al. reported that diabetic patients subjected to bariatric surgery experienced a normalization of hepatic fat content and a decrease in liver volume, as well as an increase in insulin-mediated hepatic glucose uptake, which was negatively correlated with liver fat content without any changes in BMI, suggesting a direct impact in hepatic glucose regulation [93]. Honka et al. reported that patients that underwent bariatric surgery had a decreased pancreatic lipid content and pancreatic blood flow. Glucose tolerance was found to be inversely correlated to pancreatic fat and decreased pancreatic blood flow associated to improvement of β-cell function [94].

In summary, the improvements in systemic metabolism and mainly in T2D after bariatric surgery are due to histological changes, modifications in several hormonal factors, gut microbiota composition, and their interaction. This is still under investigation, and so far, we can point out to some gut and adipose molecules as well as the microbiome, which have been associated with the amelioration of metabolic syndrome that accompanies bariatric surgery. Finally, the complex interaction between bariatric surgery, weight loss, and metabolic improvements reveals that the restriction or malabsorption components are no longer applicable to explain by themselves the effects of the surgery.

Outcomes After Metabolic Surgery

Bariatric surgery's main indication is for weight loss in individuals with obesity. Through manipulating the GI tract, bariatric surgery causes a plethora of effects that achieve substantial weight loss in a high proportion of patients. Importantly, this GI tract manipulation has effects beyond weight loss and has effects on several important metabolic disorders. In this way, bariatric surgery is a potential option for treatment for individuals with diabetes of all weights. Accordingly, this section will discuss the weight and diabetes outcomes following metabolic surgery and the implications of bariatric and metabolic surgery on other obesity-related comorbidities using an evidence-based approach.

Weight Loss After Metabolic Surgery

The weight loss component of metabolic surgery remains its most widespread indication and is the clear gold standard in the treatment of severe obesity. Patients that undergo metabolic surgery show both statistically and clinically significant weight loss soon after surgery that is maintained for several years [9, 33, 44, 95–99]. Specifically, total body weight loss at 1 year after metabolic surgery is about 25–30%, compared to 5–10% weight loss with medical therapy, and is accompanied by large reductions in body mass index (BMI) and waist circumference [33, 44, 96, 98]. At 1 year, reductions in BMI range from 19.6% to 27.6% for surgical patients compared to 1.81% to 10.14% for medical therapy patients; at 2–3 years, reductions range from 19.1% to 33.8% for surgical patients and 4.4% to 4.7% for medical therapy patients; and at 5 years, reductions range from 18.6% to 21.9% for surgical patients compared to 6.59% for medical therapy patients [9, 33, 44, 95–99]. Similarly, reductions in waist circumference at 1 year range from 17.5% to 22.8% for surgical patients and 3.6% to 7.2% for medical therapy patients; at 2–3 years, reductions range from 12.8% to 20.7% for surgical patients compared to 1.5% to 7.7% for medical therapy patients; and at 5 years, reductions range from 12.2% to 14.7% for surgical patients and 1.3% for medical therapy alone [9, 33, 44, 95, 96, 98, 99]. One of the most eminent trials in this area is the STAMPEDE trial, which randomized 150 obese patients with uncontrolled T2D to receive either intensive medical therapy alone or intensive medical therapy plus RYGB or SG [33]. A 5-year follow-up to the STAMPEDE trial showed a total body weight loss of 18% for SG and 22% for RYGB compared to 6% for medical therapy alone [9]. Moreover, metabolic surgery is much more successful than medical therapy at initiating and maintaining weight loss in morbidly obese patients with long-standing T2D.

Diabetes Remission and Main Diabetes-Associated Abnormalities Following Metabolic Surgery

Although bariatric surgical techniques have been established for the treatment of obesity by promoting weight loss and reshaping intestinal hormone signals responsible for postprandial satiety, nutrient absorption, and insulin sensitivity, the use of these techniques for the primary purpose of treating obesity-related comorbidities is still not as widely accepted compared to use primarily for weight loss. There is, however, evidence to support the use of bariatric surgical techniques in patients with T2D. With data showing that diabetic patients with obesity had increased remission rates following bariatric surgery, investigations focused on bariatric surgery to specifically manage T2D. Compiling this data in 2009, a large meta-analysis ultimately consisting of 3188 T2D patients showed that diabetes completely resolved in 78.1% of patients and either improved or resolved in 86.6% of patients following bariatric surgery [100].

Evidence from Randomized Controlled Trials

Currently, it is difficult to compare remission rates between studies as they often use different definitions of diabetes

remission and different methodologies, such as variable follow-up periods. These studies are further limited by relatively small sample sizes. While studies struggle to agree on the definitions of diabetes remission, most studies would agree that a percent glycated hemoglobin (%HbA1c) level less than 6.5% without the use of antidiabetic medication represents a T2D patient in remission. Several randomized controlled trials (RCTs) have described statistically and clinically significant differences in diabetes markers, including HbA1c, fasting plasma glucose, and homeostatic model assessment for insulin resistance (HOMA-IR) scores, between patients that receive metabolic surgery and those that receive intensive medical therapy [8, 33, 96, 101]. These studies primarily examined RYGB, biliopancreatic diversion with duodenal switch (BPD-DS), or SG in which their 1-year diabetes remission rates range from 35% to 44% for surgical patients compared to 0% to 9% for medical therapy patients, their 2-year remission rates range from 21.6% to 89.5% for surgical patients compared to 0% to 5.9% for medical therapy patients, and their 5-year remission values were also extremely variable with rates ranging from 18.8% to 50% for surgical patients compared to 0% for medical therapy patients [8, 9, 33, 95, 96, 101]. However, in spite of the large variation in remission rates, metabolic surgery consistently outperforms intensive medical therapy alone for the management of T2D in these RCTs.

Renal Changes and Micro-/Macrovascular Complications

When looking at diabetes-related complications, the STAMPEDE trial showed that there were either minimal or no changes to the measures of renal function, such as glomerular filtration rate (GFR), albuminuria, or creatinine-to-albumin ratio [95]. Conversely, Du et al. found that in patients with class 2 or 3 obesity, hyperuricemia was either resolved or improved in about 73% of patients following metabolic surgery, compared to 4% of class 1 obese patients [102]. These results would suggest that higher BMI subjects could benefit more from metabolic surgery in terms of positive renal changes; however, there is little evidence to validate this finding.

Microvascular complications, including retinopathy, nephropathy, and neuropathy, and macrovascular complications, including coronary artery disease, cerebrovascular disease, and peripheral artery disease, can occur in T2D patients with long-standing disease. Prospectively collected data on the attenuation or reduced risk of micro- and macrovascular complications is limited. However, among the 603 patients with T2D in the Swedish Obese Subjects (SOS) study, there were a 56% and a 32% decreased incidence of micro- and macrovascular complications, respectively, following bariatric surgery compared to the medical therapy group at a 15-year follow up [103]. Similarly, the incidence of microvascular complications was 59% lower in bariatric surgery patients compared to nonsurgical controls in a retrospective matched cohort study including 4024 surgical patients with a median follow-up of 4.3 years [104]. Further, a 2021 meta-analysis found that bariatric surgery reduced macrovascular complications by 50% with a mean follow-up time of 10.96 years [105].

Outcomes of Other Comorbidities Associated with Obesity and Metabolic Syndrome Following Metabolic Surgery

In addition to diabetes, there is evidence that metabolic surgery improves other obesity-related comorbidities, such as hypertension, dyslipidemia, and cardiovascular diseases. The research into the effect of bariatric surgery on these other comorbidities is often secondary to diabetes outcomes. As such, one cannot state conclusively whether metabolic surgery improves these conditions and whether the amelioration of these conditions is strictly due to weight loss or is also dependent on weight loss-independent mechanisms. We can, however, comment on the current state of knowledge regarding the impact of metabolic surgery on various test parameters, including blood pressure and serum lipid levels, to preliminarily assess the potential of metabolic surgery in attenuating obesity-related comorbidities.

Hypertension

Hypertension is one of the components that comprise "metabolic syndrome." As a major risk factor for cardiovascular and renal diseases, blood pressure management is imperative to prevent the development of other complications. Prevention or management of high blood pressure can be achieved by also managing weight. Metabolic surgery generally decreased systolic blood pressure (SBP) with reductions ranging from 12 mmHg to 34 mmHg [44, 96, 97, 99], while diastolic blood pressure (DBP) had reductions ranging from 5 mmHg to 10 mmHg [44, 96, 99]. A retrospective study found that metabolic surgery resolved or improved hypertension in 60% of class 2 or 3 obese subjects and 20% of class 1 obese subjects at 3 years postoperatively [102]; however, due to the small sample size, these results were not significant. In the STAMPEDE trial, neither SBP nor DBP was reduced by metabolic surgery at 1, 3, or 5 years, but there was a significant decrease in the number of antihypertensive medications required to manage the disease [9, 33, 95]. Similar results were found in a small RCT with no changes in SBP or DBP at 1 year following metabolic surgery [98], and another RCT showed reductions in antihypertensive medications following RYGB [97]. Any changes in blood pressure following

metabolic surgery are still controversial, yet it appears that those who receive metabolic surgery require less medical management of hypertension.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is an obesity-related disorder that increases the risk of hypertension development. Several studies have found that a large proportion of bariatric surgery patients show improvement in the number of sleep disturbances, sleep efficiency, and the severity of OSA [106–109] while others show no change in polysomnographic variables in the years after bariatric surgery [10]. A systematic review of OSA outcomes following bariatric surgery including 69 studies and 13,900 patients saw that BPD-DS, followed by SG, RYGB, and finally LAGB, had the most improvement in OSA postoperatively [107]. In fact, 99% of BPD-DS patients saw improvement in their OSA, compared to 85.7% for SG, 79.2% for RYGB, and 77.5% for LAGB [107]. Bariatric surgery has quite promising results in attenuating OSA symptoms. While unlikely to be the primary objective for performing bariatric surgery, improvement of OSA is a favorable secondary effect.

Dyslipidemia

Abnormal serum lipid levels are also a condition of metabolic syndrome. Typically, we see higher low-density lipoprotein (LDL) cholesterol and triglycerides (TG) and lower high-density lipoprotein (HDL) cholesterol in metabolic syndrome. In articles that categorically assessed dyslipidemia incidence before and after metabolic surgery, dyslipidemia was resolved in about 50% of patients at 1 year and 59% at 3 years [98, 102]. Within the first 1–5 years following metabolic surgery, there are consistent results of elevated HDL cholesterol to acceptable levels (≥45 mg/dL or 1.17 mmol/L) and decreased TGs to optimal levels (<150 mg/dL or 1.7 mmol/L), which is not observed in the medical therapy group [9, 33, 44, 96, 97, 110]. In regard to LDL cholesterol, the results are discrepant between studies. Several studies did not observe any changes in LDL cholesterol from baseline to their respective follow-up period in either the metabolic surgery recipients or those receiving medical therapy [9, 95, 96]. However, appropriate LDL reductions have also been observed following metabolic surgery in other studies [44, 97]. Particularly, one study showed that BPD-DS reduced LDL cholesterol and TGs to clinically optimal levels (<2.6 mmol/L or 100 mg/dL for LDL cholesterol), but this was not observed in the patients that received RYGB surgery. Reductions in LDL cholesterol following BPD-DS have also been reported in other studies [110, 111]. While some techniques, including RYGB, may normalize serum lipid levels apart from LDL cholesterol, it is possible that BPD-DS can achieve optimal LDL cholesterol reductions. At the 1-, 3-, and 5-year follow-ups in the STAMPEDE trial, the use of lipid-lowering medications by metabolic surgery recipients decreased by 60%, 56%, and 43% from baseline, respectively, with no changes in lipid-lowering medications by the patients receiving medical therapy only [9, 33, 95].

Cardiovascular Disease

Cardiovascular disease (CVD) is the leading cause of death worldwide, and both obesity and T2D can greatly increase the risk for CVD development. A group from the United States sought to determine if metabolic surgery can protect obese T2D patients from CVD with their retrospective cohort study of over 2200 diabetic patients with obesity undergoing metabolic surgery compared to over 11,000 matched controls. Looking specifically at major adverse cardiovascular events (MACE) over an 8-year period, this group found that metabolic surgery recipients had a hazard ratio of 0.61 compared to controls [112]. This suggests that metabolic surgery patients with both obesity and diabetes were about 40% less likely to experience a MACE in the first 8 years after surgery. A 2021 propensity score matched study of 2638 patients assessing bariatric surgical patients and nonsurgical controls with severe obesity and cardiovascular disease showed similar success with a hazard ratio of 0.58 for surgical patients compared to the nonsurgical controls [113]. In subgroup analyses of patients with a history of heart failure or ischemic heart disease, bariatric surgery reduced the incidence of MACE by 56% and 40%, respectively [113]. In addition to this, in terms of individual cardiovascular events, metabolic surgery patients had a much lower incidence of heart failure, coronary artery disease, cerebrovascular disease, nephropathy, and atrial fibrillation [112]. Moreover, the use of antidiabetic, antihypertensive, and lipid-lowering medications was significantly reduced in metabolic surgery patients [112], further corroborating the observations of the STAMPEDE trial.

Special Topics

Apart from the conventional use for metabolic surgery in T2D patients with a BMI ≥ 35 kg/m^2, physicians have started to apply these surgical techniques to different populations, such as in T2D patients with a BMI < 35 kg/m^2 or in type 1 diabetic (T1D) patients. Moreover, current studies are aiming to identify which type of bariatric surgery is the most effective for diabetes remission and to determine the long-term outcomes following metabolic surgery. These special topics serve as the future of metabolic surgery research and application to target populations.

The Use of Metabolic Surgery in Type 2 Diabetes Patients with a BMI < 35 kg/m²

Bariatric/metabolic surgery is typically only performed in patients with a BMI ≥ 35 kg/m² and long-standing diabetes. While the use of metabolic surgery is still controversial in overweight and class 1 obese patients, the idea that metabolic surgeries may be used to manage uncontrolled T2D in these patients is becoming more popular. In metabolic surgery patients with a BMI < 35 kg/m², clinically significant reduction in BMI, weight, and waist circumference has been observed as early as 6 months after surgery [114]. This effect is seen following various metabolic surgery techniques, including RYGB [98, 102, 114–120], BPD [121], SG [114, 122], one anastomosis gastric bypass (OAGB), [122] and LAGB [98, 114, 123]. Additionally, a reduced BMI is often maintained for several years following metabolic surgery in class 1 obese patients [102, 117, 121, 122]. Most studies that compare metabolic surgery to other anti-obesity or antidiabetic standard-of-care treatments, such as GLP-1 analogs, intensive medical therapy, lifestyle interventions, and SGLT2 inhibitors, also show marked reductions in anthropometric variables with metabolic surgery compared to the pharmacological or lifestyle interventions [98, 114, 116, 123].

What should be noted, however, are the comparisons between class 1 obesity and class 2/3 obesity weight outcomes following metabolic surgery. The changes in weight loss are not absolute in obesity patients. Instead, all three classes of obesity tend to exhibit comparable BMIs for several years following surgery [102]. While remaining clinically significant, it appears that patients with a higher preoperative BMI achieve greater anthropometric effects postoperatively compared to overweight or class 1 obese metabolic surgery patients. Thus, to assess and compare the benefits of metabolic surgery between different classes of obesity, we must explore the outcomes of diabetes following surgery in this population.

A retrospective review found no difference in diabetes remission rates between class 1 and class 2/3 obese patients at 1- or 3-year follow-up [102]. However, while some may argue that metabolic surgery is more efficacious for the management of diabetes in patients with a higher preoperative BMI, it needs to be determined whether metabolic surgery is also reasonably more effective than standard medical and lifestyle interventions in patients with a BMI lower than 35 kg/m². From data in RCTs and prospective studies in this population, diabetes remission rates within 1 year of surgery range from 51 to 65% and somewhere around 26 and 84% between 18 months and 5 years after surgery [102, 114, 115, 118, 120–122]. In the few studies that compared remission rates after metabolic surgery to medical therapy, the diabetes remission rates in the medically treated groups were either nonexistent or significantly lower at 0–6% [114, 118, 120]. Notably, these studies are limited by small sample sizes and poor follow-up. Regardless, although there is debate on whether higher classes of obesity may or may not exhibit greater benefits from metabolic surgery than lower classes, these preliminary results show that the benefits that are observed in T2D patients with a BMI < 35 kg/m² remain superior to medical therapies. Instead of comparing between classes of obesity, a "cut-off point," which defines a certain weight category that no longer attains higher diabetes remission rates than medical therapies, should be determined.

Metabolic Surgery in Type 1 Diabetics

Obesity is common in T2D patients and increases the risk for the development of diabetes [124]. However, obesity is rarer in T1D patients, although a subset of T1D patients is overweight [125]. Moreover, intense insulin treatment may make patients more susceptible to weight gain [126, 127]. By examining the outcomes of bariatric surgery in obese patients with T1D, we can begin to assess the viability of metabolic surgery in this population. A systematic review and meta-analysis of outcomes following bariatric surgery in obese T1D patients show clinically significant weight loss [128]. In addition to this, although bariatric surgery reduced daily insulin requirements, insulin therapy was still required [128]. This can be explained since T1D patients have little to no β-islet cell activity to produce their own insulin. Bariatric surgery also decreased HbA1c levels, but only to 7.9 ± 1.1% [128]; these levels remain quite elevated and are not indicative of diabetes remission, in spite of the statistically significant improvement. Further investigation into the efficacy of metabolic surgery in T1D patients is warranted, but based on these preliminary results, the efficacy of surgery is unclear and may be considered draconian relative to the extent of diabetes remission.

The suggested mechanisms for improved glycemic control and reduced insulin requirements are similar to those in T2D metabolic surgery patients. Weight may ameliorate obesity-related insulin resistance via reduced lipotoxicity and inflammation [128]. Although studies in this area are small and limited, there is some evidence to suggest that insulin requirements following bariatric surgery are not directly correlated to weight loss, indicating that there are other mechanisms for improved glycemic control independent of weight loss [129]. Reduced insulin requirements may be simply due to decreased caloric intake and glycemic load. Further, increased incretin release due to the hindgut hypothesis may inhibit the actions of glucagon and even potentiate insulin activity in patients with residual β-islet cell function [130]. Regardless, mechanisms that reduce insulin sensitivity and potentiate the actions of insulin will allow for the mitigation of excessive exogenous insulin use. Kirwan et al.

report that bariatric surgery results in the remission or improvement of many obesity-related comorbidities, including hypertension and dyslipidemia [128]. A single, small retrospective study comparing BPD-DS and SG recipients found that T1D and T2D patients had similar remission rates of hypertension and dyslipidemia [131]. Therefore, although the use of metabolic surgery to induce remission of diabetes in T1D patients is contentious, there is currently no contraindication for the use of these techniques in obese patients with T1D or obesity-related comorbidities.

Diabetes Remission and Relapse Using Different Types of Metabolic Surgery

With such a wide array of different bariatric surgical techniques, it is difficult to parse out which may be the most effective in terms of diabetes remission based on the hundreds of studies with consistent or contradictory findings. The 2009 meta-analysis by Buchwald et al. showed that diabetes remission rates are maintained at a 2-year follow-up with BPD-DS at 95.1%, RYGB at 80.3%, then gastroplasty at 79.7%, and finally LAGB at 56.7% [100]. The relationships between different techniques are echoed in a 2020 network meta-analysis of RCTs evaluating diabetes remission following metabolic surgery in patients with follow-ups greater than 3 years with rank probabilities of remission at 91.3% for BPD-DS, 84.2% for OAGB, 58.4% for RYGB, 39.9% for SG, and 24.9% for LAGB [132]. Notably, the remission rates for RYGB and LAGB were substantially lower in the 2020 study compared to the study conducted in 2009.

Using RCTs, we can also evaluate the relapse rates of diabetes for the various techniques. BPD-DS had a 37% relapse rate between postoperative years 2 and 5 [8]. RYGB had moderate relapse rates with 25% relapse between years 1 and 2 [101], 53% relapse between years 2 and 5 [8], and 47.6% relapse between years 1 and 5 [9, 33]. On the other hand, SG had 60% diabetes relapse between postoperative years 1 and 2 [101] and about 46% relapse between years 1 and 5 [9, 33].

Even though LAGB is not performed as widely as it was a decade ago, this technique can be compared to the more modern surgeries. While diabetes remission does not typically correlate directly to weight loss following metabolic surgery as stated earlier in this chapter, RCTs using LAGB to attenuate diabetes have shown weight loss is the major force promoting diabetes remission [123, 132, 133], likely due to a lack of considerable anatomical reconstruction of the GI tract. This may also explain why surgeries like BPD-DS, RYGB, and SG typically perform better than LAGB.

Patients appear to exhibit the highest diabetes remission rates and the lowest relapse following BPD-DS compared to the other surgical techniques. In a 2005 review of 312 obese T2D BPD-DS patients, over 99% of patients achieved diabetes remission at 1 year, and there was only a 2% relapse rate over 10 years [110]. These values are drastically higher than those reported in the RCTs and meta-analyses; regardless, BPD-DS is consistently the most effective in terms of both weight loss and diabetes remission rates; however, this technique is not used as frequently worldwide due to its inherent technical challenges and there is also a higher risk of complications including nutritional deficiencies when the proximal small intestine is bypassed [134]. While more research into this area is definitely needed, there is a strong potential for successful treatment of diabetes using bariatric surgical techniques.

Long-Term Outcomes of Metabolic Surgery

One of the strongest available long-term studies on T2D remission is the SOS study [103]. This prospective matched cohort study examined diabetes remission for non-adjustable gastric banding (NGB), vertical banded gastroplasty (VBG), and RYGB versus standard diabetes and obesity care over a 15-year period. T2D remission rates at 2 years after surgery were 16.4% for medical therapy patients and 72.3% for bariatric surgery patients. At 15 years, diabetes remission rates decreased to 6.5% for medical therapy patients and to 30.4% for bariatric surgery patients. There is a high relapse in diabetes remission from 2 to 5 years; however, remission rates were still much greater in the bariatric surgery group compared to the medical therapy group. In addition to this, the risk of both macro- and microvascular complications was significantly reduced in those that had bariatric surgery.

A recent retrospective study of insulin-treated T2D patients that received BPD-DS showed substantial diabetes remission rates 10 years after metabolic surgery with up to 68% of patients in complete remission [135]. Importantly, those with a shorter disease duration at the time of surgery were more likely to achieve complete diabetes remission compared to those with longer disease duration [135]. As metabolic surgery is seldom going to be a primary management strategy for diabetes, earlier diagnosis and treatment will be an important factor in order for patients to have the best chances of achieving remission with metabolic surgery.

Complications After Bariatric/Metabolic Surgery

Bariatric/metabolic surgery is considered extremely safe nowadays, even as safe as a laparoscopic cholecystectomy [136]. Morbidity and mortality rates have decreased dramatically since the introduction of the laparoscopic approach, as well as the evolution of technology, understanding of

associated diseases, and perioperative management of patients [137]. In order to standardize the way in which complications in bariatric surgery should be reported, their classification by temporality and severity has been established [138]. Early complications are those that occur within the first 30 days, and after that, they are considered late complications. By severity, they are divided into minor and major, with the major generally being those that cause early reintervention, bleeding that requires blood transfusions, need for ICU, and hospital stay longer than 7 days. The most common complications appear during this period, being mainly bleeding (intra-abdominal or gastrointestinal), leak/fistula, and stenosis, which is observed in approximately 2–19% of cases (there is variability depending on the type of procedure [139, 140]). Deep vein thrombosis (DVT) and pulmonary embolism (PE) can also occur within this period but are less frequent. Mortality should not exceed 0.1–0.5% [136]. In terms of late complications, the RYGB has been associated with a greater cause of readmissions and a greater number of complications compared to SG [141]. The most observed pathologies during follow-up are cholelithiasis, marginal ulcers, internal hernias, reflux, and nutritional deficiencies. Some of the factors associated to higher morbidity are open procedures, extreme obesity, previous DVT/PE, sleep apnea, revisional surgery, and surgeries performed at low-volume hospitals [142].

Even though bariatric surgery, with the upcoming technologies, has proved to be a safer procedure, less invasive and novel patient-targeted approaches are being developed in order to decrease current rates of complications, morbidity, and mortality.

Evolving Technologies for Metabolic Treatment

The prevalence of obesity is continuously increasing worldwide with an accentuation during the current COVID-19 pandemic. Currently, bariatric surgery represents the best option for the treatment of obesity and its related metabolic comorbidities. Importantly, only a small fraction of the eligible population undergoes bariatric surgeries even in those countries with well-established bariatric surgery centers.

Recently, various endoscopic treatments have evolved with the goal of offering minimally invasive options for a greater number of patients suffering from obesity as well as diabetes [143]. Although not currently FDA approved, these interventions might represent viable options in the future somewhere in the continuum of care between bariatric surgery and pharmacotherapy and lifestyle interventions. These metabolic endoscopic interventions may offer a different therapeutic perspective than the well-established gastric space-occupying devices and endoscopic gastric suturing procedures.

Currently, there are three main types of endoscopic small bowel interventions that could have a significant impact in patients with metabolic syndrome: endoscopic anastomosis systems, duodenal mucosal resurfacing systems, and finally endoluminal bypass liner systems.

Endoscopic Magnetic Compression Anastomotic Devices

Endoscopic therapies trying to replicate the weight loss and metabolic results of the SADI-S procedure have been described. The Incisionless Magnetic Anastomosis System (IMAS-GI Windows, West Bridgewater, MA, United States) relies on a magnet that is introduced through the working channel of the endoscope and takes its final octagonal form when deployed into the lumen. A recent case series of eight patients with a BMI of 35–47 and T2D illustrated the feasibility of a combined laparo-endoscopic procedure [144]. The proximal magnet was inserted endoscopically and positioned 2 cm distal to the pylorus, while the distal magnet was inserted laparoscopically through a 5 mm enterotomy 300 cm proximal to the ileocecal valve. The magnets were expelled per rectum at a median of 29.5 days post procedure with no complications. All anastomoses were patent at 1 year. The baseline HbA1c was reduced below 7% in 75% of patients, and greater than 5% of total body weight loss was seen in 87.5% of patients at 12 months [144].

The Magnamosis device (Magnamosis Inc.) is a pair of rare earth magnets encased in a polycarbonate shell [145]. Following multiple successful animal studies, a first-in-human trial was published in 2017. This case series included five patients. The surgical procedures were performed through laparotomy in complex urology cases requiring the creation of an ileal conduit. One small bowel side-to-side anastomosis was created in each case with a central hole being performed surgically to obtain immediate patency. No complications such as anastomotic leaks, bleeding, or stenosis were noted during the 13-month median follow-up (range: 6–18 months). Although no metabolic interventions were attempted to date using this device, Magnamosis Inc. has recently been awarded an NIH grant to study the effect of a Magnetic Duodeno-Ileal Bypass (DIPASS) on T2D in a primate model [146].

Finally, a third device, EasyByPass (EasyNOTES) [147], uses neodymium rare earth magnets that are placed endoscopically to create a gastrojejunal anastomosis under fluoroscopy and with the help of a large external magnet [143]. A few weeks following the creation of the new anastomosis, a pyloric plug is inserted endoscopically to divert the gastric contents through the new gastrojejunostomy [147]. There is

currently no published data on the use of this device in animal or human studies.

Duodenal Mucosal Resurfacing

The Revita duodenal mucosal resurfacing (DMR) procedure is a minimally invasive endoscopic procedure in which the mucosa distal to the ampulla of Vater is thermally ablated using a specially designed catheter (Fractyl Laboratories, Lexington, MA, United States) that is advanced over a guidewire under endoscopic guidance. Following a mucosal saline lift, a sequential ablation of the duodenal mucosa is performed for about 10 cm distal to the ampulla [148]. In a recent international multicenter study, the effect of DMR was studied in patients with T2D treated with at least one oral hypoglycemic medication and with a BMI ranging from 24 to 40 kg/m^2 [149]. The procedure was completed in 80% of patients. There was only one significant adverse event: fever with spontaneous resolution. Mean HbA1c was 10 mmol/mol (0.9%) lower at 1 year post DMR compared to baseline. There was some weight loss at 4 weeks post procedure with weight stabilization afterward. No correlation between the weight loss and glycemic control was noted.

Another DMR device, DiaGone (Digma Medical, Petah Tikva, Israel), uses a precisely controlled laser technology to target the duodenal submucosal neural plexi [150]. The results of a small multicenter feasibility study were published in an abstract in 2019 [151]. Nine patients with a BMI of 34.0 ± 4.6 kg/m^2 and T2D with insufficient glycemic control on metformin were enrolled. A significant decrease ($p < 0.01$) in fasting glucose (12.4 mmol/L baseline to 9.5 and 9.7) and HbA1c (7.83% mmol/mol baseline to 6.4% and 6.48%) was noted at 3 and 6 months following the procedure. No adverse events nor change in weight was noted during the 6-month follow-up [151].

Endoluminal Bypass Liners

Currently, there are two types of endoluminal "sleeve" systems that share the same mechanism of prevention of contact between the gastric contents and the proximal small bowel and possibly alterations in gut microbiota [143, 152] (Table 42.2).

Duodenal-Jejunal Bypass Liner

The first system is the duodenal-jejunal bypass liner EndoBarrier (DJBL – GI Dynamics, Lexington, MA, USA). EndoBarrier is a 60 cm fluoropolymer liner that is placed under endoscopic and fluoroscopic control. The proximal nitinol anchor is deployed in the duodenal bulb with the liner released distally into the small bowel [150]. It is removed endoscopically after 3–12 months. A meta-analysis published in 2018 that included 17 studies evaluating EndoBarrier has shown an overall 18.9% total body weight loss and a 1.3% reduction in HbA1c. The weight loss was shown to be still significant at the 12-month follow-up post device explantation [153].

Table 42.2 Current endoscopic metabolic interventions targeting the small intestine [143]

Endoscopic small bowel interventions	Clinical options
Endoscopic anastomotic devices	IMAS: Incisionless Magnetic Anastomosis System (GI Windows) Magnamosis (Magnamosis Inc.) EasyByPass incisionless anastomosis device (EasyNOTES)
Duodenal mucosal resurfacing systems	Revita (Fractyl Laboratories) DiaGone (Digma Medical)
Endoluminal bypass liner systems	Duodenal-jejunal bypass liner (DJBL – GI Dynamics) Gastro-duodenal bypass liner (ValenTx Endoluminal Bypass)

Notwithstanding the excellent results published in the previous studies, a multicenter controlled trial in the United States had to be terminated early when 3.5% of patients developed hepatic abscesses [154]. Recently, the largest multicenter randomized controlled study of DJBL was published [155]. The study enrolled 170 patients with inadequately controlled T2D and obesity that were subsequently randomized to intensive medical care with or without DJBL. Interestingly, there was no significant difference in the percentage of patients achieving a HbA1c reduction of ≥20% at 12 months (primary outcome). There was, however, greater weight loss in the DJBL group (24% of patients achieved ≥15% weight loss in the DJBL group compared to only 4% in the intensive medical care group at 12 months). Better reduction in systolic blood pressure, cholesterol levels, and alanine transaminase was noted at 12 months. There were 19 early explantations of the DJBL, and these were caused by seven cases of migration of the device, abdominal pain in five patients, upper gastrointestinal bleeding in two patients, cholecystitis in two patients, and a single case of liver abscess, anticoagulation, or withdrawal of consent. The hepatic abscess resolved following explantation of the device and percutaneous drainage of the abscess. One explantation had to be performed laparoscopically as the endoscopic removal failed [155]. Although there was no improved glycemic control, the improvement in weight and other comorbidities together with the lower rate of hepatic abscess (1.3%) is encouraging. The large US STEP-1 FDA-approved trial is currently actively recruiting patients, and this will hopefully generate valuable information about the efficacy and safety profile of DJBL.

Gastro-duodenal Bypass Liner

The second system is the gastro-duodenal bypass liner system (ValenTx Endoluminal Bypass, Maple Grove, MN, USA). This device has twice the size of the DJBL (120 cm) with the proximal part being anchored at the gastroesophageal junction. It is designed to reproduce some of the restrictive and hypoabsorptive characteristics of a classic laparoscopic gastric bypass. The initial human experience reported in 13 patients showcased impressive results with a 54% excess weight loss and >70% improvement in associated comorbidities after 12 months [156]. Only four of these patients had T2D; 3/4 had more than 1% improvement in Hb1Ac, and 1/4 had significant improvement *with cessation of hypoglycemic treatment* [156]. Despite these encouraging results, early device removal was necessary due to odynophagia and intolerance in 17% and 23% of cases, respectively [156, 157]. In a more recent multicenter international study, 32 patients with a mean BMI of 42.3 kg/m^2 were enrolled into a single-arm feasibility trial [158]. Eighty-eight percent of devices remained implanted after 12 months, with notable adverse events including knotting of the sleeve in two patients, distal migration of the device requiring removal through laparotomy in one patient, and esophageal food impaction in one patient. Although no metabolic data was published, subjects lost on average 17.6% total body weight and 44.8% excess body weight at 12 months. Ongoing device development and further clinical investigations are currently underway.

Multiple Choice Questions

1. What is the gold standard bariatric/metabolic surgery?
   (a) LAGB
   (b) SG
   (c) **RYGB**
   (d) BPD-DS
2. What is the most commonly performed bariatric surgery worldwide?
   (a) LAGB
   (b) **SG**
   (c) RYGB
   (d) BPD-DS
3. What are the main surgeries that promote decreased ghrelin and an increase of GLP-1 and YY?
   (a) LAGB and SG
   (b) SG and RYGB
   (c) **RYGB and BPD-DS**
   (d) BPD-DS and LAGB
4. What is the main orexigenic hormone that is suppressed after sleeve gastrectomy?
   (a) Adiponectin
   (b) Leptin
   (c) **Ghrelin**
   (d) PYY-GLP-1
5. What hormone, which increases after RYGB, is associated with insulin resistance and appetite?
   (a) Adiponectin
   (b) Leptin
   (c) Ghrelin
   (d) **GLP-1**
6. Which of the following is an indication for bariatric surgery?
   (a) Obesity class 1
   (b) Obesity class 2 without comorbidities associated
   (c) **Obesity class 3 even when no comorbidities are associated**
   (d) BMI > 30 kg/m^2 and metabolic syndrome
7. According to the Standards of Care for Diabetes algorithm, when can metabolic surgery be considered?
   (a) Obesity class 1
   (b) **Diabetic subjects with inadequately controlled hyperglycemia despite medical treatment in subjects with a BMI ranging from 30 to 34.9 kg/m^2**
   (c) Overweight patients with uncontrolled diabetes
   (d) Metabolic surgery is not currently considered as an option for treatment
8. What changes in the composition of gut microbiota are associated after RYGB?
   (a) **Increased presence of Proteobacteria and Bacteroidetes**
   (b) Increase in Bacteroidetes and Firmicutes
   (c) Decrease in Firmicutes and Proteobacteria
   (d) Increase in *Lactobacillus* and Firmicutes
9. What is the adipokine that communicates between adipose tissue and the CNS to suppress food intake during energy sufficiency and decreases after bariatric surgery?
   (a) Adiponectin
   (b) GLP-1
   (c) **Leptin**
   (d) PYY

Glossary

Adipokines Hormones that are released from adipose tissue. The most well-known adipokines are leptin and adiponectin.

Bariatric Surgery Type of surgery that involves changes in the digestive system (restriction or redirection) in order to achieve weight loss and metabolic improvement

Incretins Intestinal peptides known for stimulating insulin production after food intake. The main incretins are PYY and GLP-1.

Laparoscopic surgery Minimal invasive surgery where trough small incisions (5–10 mm), ports are placed, CO_2 is insufflated, a camera (that transmit imagen from abdominal cavity to a monitor) and specialized instruments are inserted to perform a surgery. This type of surgery has the

advantage to be faster and less invasive compared to open approach and facilitates a faster recovery.

Obesity Abnormal or excessive fat accumulation that presents a risk to health. It is considered when BMI is ≥30 kg/m^2.

Obesity Class 1 Patients with a BMI ranging from 30 to 34.9 kg/m^2

Obesity Class 2 Patients with a BMI ranging from 35 to 39.9 kg/m^2

Obesity Class 3 Patients with a BMI of 40 kg/m^2 or greater

Roux-en-Y Gastric Bypass Gold standard bariatric surgery that involves a re-routing of the passage of food. A small gastric pouch is created and connected to the jejunum, "bypassing" the stomach, the duodenum, and the first portion of the jejunum. After the surgery, a decrement in ghrelin and GIP and an increase of GLP-1 and PYY are observed.

Sleeve Gastrectomy Vertical transection of the stomach, starting at the greater curvature at 6 cm proximal to the pylorus toward the angle of His. It is performed with a laparoscopic stapler, guided over a 32Fr orogastric tube. It decreases the amount of food intake, ghrelin concentrations, and appetite and increases intragastric pressure.

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Diabetes and Smoking: The Burden of Evidence

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Introduction

Smoking has been identified as the leading preventable risk factor for premature mortality and morbidity. Large volumes of literature are now available linking smoking with cardiovascular morbidity and mortality, diabetes, vascular damage, cancers, and neurocognitive dysfunction, among others. It will not be erroneous to state that every system of the body is affected by smoking. Smokers die on average 8–10 years younger than nonsmokers. This chapter intends to highlight the complex relationship between smoking and the occurrence and the associated morbidity related to diabetes.

Smoking and Diabetes: Incidence and Mechanism

The impact of smoking on glycemia is complex. Smoking is strongly linked with both increased incidence and severity of diabetes. Smoking cessation, at least in the short term, is associated with weight gain, which is also associated with increased incidence of diabetes.

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The risk of developing diabetes in smokers has been found to be dose dependent. A meta-analysis of 25 studies reported that heavy smokers (smoking ≥20 cigarettes/day) were more likely to develop diabetes (relative risk (RR) = 1.61; 95% CI = 1.43–1.80) as compared to light smokers (RR = 1.29; 95% CI = 1.13–1.48) and former smokers (RR = 1.23; 95% CI = 1.14–1.33). A study on industrial workers in a large cohort of individuals in Taiwan showed that compared to never-smokers, both current smokers and ex-smokers in their first 2 years of abstinence had higher odds ratios (ORs) for newly diagnosed diabetes mellitus (never-smokers 3.6%, OR = 1; current smokers 5.5%, OR = 1.499, 95% CI = 1.147–1.960, and $p = 0.003$; ex-smokers in their first year of abstinence 7.5%, OR = 1.829, 95% CI = 0.906–3.694, and $p = 0.092$; and ex-smokers in their second year of abstinence 9.0%, OR = 2.020, 95% CI = 1.031–3.955, and $p = 0.040$) [1]. This higher incidence of diabetes in ex-smokers was independent of the associated weight gain [1].

Smoking is found to cause diabetes by insulin resistance as well as decreased insulin release due to pancreatic β-cell damage by inflammatory and oxidative pathway mechanisms. Another concerning fact is that fetal exposure to smoking (maternal smoking during pregnancy) is associated with increased risk of diabetes later in life [2]. The silver lining is the observation that a healthy lifestyle intervention can go a long way in reducing this risk of diabetes among these persons [2].

Smoking is associated with increased and differential DNA methylation of type 2 diabetes genes, especially the ANPEP, KCNQ1, and ZMIZ1 genes, which may explain how smoking is associated with long-term increased diabetes risk [3].

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Smoking and Non-microvascular or Non-macrovascular Complications

Smoking is an independent predictor of atherosclerosis. It has a stronger association with postprandial dyslipidemia and not fasting lipid values. It has been linked with postprandial hypertriglyceridemia [4].

Smoking and Microvascular Complications of Diabetes

Smoking increases the risk for microvascular complications of diabetes, probably via its metabolic effects in combination with increased inflammation and endothelial dysfunction [5]. This association is strong in type 1 diabetes patients and seen for all microvascular complications. However, the association of smoking with microvascular complications in type 2 diabetes is comparatively weaker except for nephropathy. Studies have clearly supported the negative impact of smoking on diabetic kidney disease in type 2 diabetes too, but its independent influence on retinopathy and neuropathy in type 2 diabetes remains unclear [5].

Smoking and Diabetic Nephropathy

Several studies have demonstrated that smoking promotes the development and progression of diabetic nephropathy in persons with both type 1 and type 2 diabetes, and smoking is an independent risk factor for diabetic kidney disease. Also, smoking is associated with an increased risk for end-stage renal disease and decreased survival on commencement of dialysis. In a 13-year follow-up study by Biesenbach et al., the progression of diabetic nephropathy was clearly increased in smokers. Other prospective studies have also confirmed more frequent diabetic nephropathy in smokers than nonsmokers. Continued smoking has shown to be associated with further poor renal outcome as compared to persons who quit smoking. Smoking adversely affects renal hemodynamics and protein excretion even in subjects without apparent renal disease. In addition, it impairs the prognosis for renal function in patients with nondiabetic renal disease. Factors implicated in the pathogenesis of smoking-induced renal function impairment are the sympathetic activation, increased endothelin production, increased oxidative stress, and impaired endothelial cell-dependent vasodilation [6]. Cessation of smoking has been associated with slower progression of the nephropathy and, as an alone measure, may reduce the risk of progression by 30% in patients with type 2 diabetes.

Smoking and Diabetic Retinopathy (DR)

Smoking has a profound negative impact on overall eye health in diabetes [5]. Smoking has been implicated in the development and progression of numerous ocular diseases, including age-related macular degeneration, glaucoma, and cataracts. Chronic smoking has been shown to be associated with decreased retinal circulation as well as abnormalities in the retinal vessel parameters. Smoking leads to a higher incidence of and accelerated progression of diabetic retinopathy (DR) in patients with type 1 diabetes. However, in type 2 diabetes, evidence is controversial in context of smoking and DR. The Hoorn study demonstrated a nonsignificant trend for increased DR incidence in cigarette smokers as well as ex-smokers. Another, 25-year follow-up study showed a nonsignificant trend of developing more proliferative DR in current smokers. However, there was no statistically significant association between smoking status or pack-years of smoking and proliferative DR. In the same study, mild NPDR was more common among current smokers than former smokers, which may suggest that smoking is indeed related to early forms of diabetic retinopathy. However, many studies have reported no association with smoking and retinopathy in type 2 diabetes. Rather the United Kingdom Prospective Diabetes Study (UKPDS) study demonstrated a protective effect of smoking on both new development and progression of DR. Thus in type 2 patients, the effects of smoking on DR is more complex and yet to be fully elucidated [6].

Smoking and Diabetic Neuropathy

Like the association of smoking and retinopathy, there is evidence that smoking is an independent risk factor of peripheral neuropathy in patients with type 1 diabetes [7]. However, the association of smoking with neuropathy in type 2 diabetes is not clear. Surprisingly, a protective effect of smoking has been reported in few studies. In other studies with patients with type 2 diabetes, smoking was not a risk factor for the polyneuropathy or sensory neuropathy as diagnosed by symptoms and signs. A meta-analysis including 10 prospective and 28 cross-sectional studies has found that smoking had an unadjusted odds ratio of 1.26 for prospectively developing diabetic sensory polyneuropathy. In the cross-sectional studies, the pooled odds ratio for diabetic sensory polyneuropathy due to smoking was 1.42. However, for both analyses, evidence was graded as low strength. More studies are needed to evaluate the association between smoking and neuropathy [7].

Smoking and Macrovascular Complications of Diabetes

Smoking has been shown to be a significant risk factor for all-cause mortality, and for mortality due to cardiovascular disease (CVD) and coronary heart disease (CHD) in patients with diabetes.

Coronary Artery Disease

Smoking is a major risk factor for CVD in nondiabetic subjects, as well as diabetic subjects. In the London cohort of the 8-year prospective, World Health Organization Multinational Study of Vascular Disease in Diabetes, it was shown that smoking is significantly associated with an increased risk for coronary heart disease (CHD) in type 1 and type 2 diabetes patients [8]. In the Diabetes Control and Complications Trial (DCCT), designed to study the role of intensive insulin treatment and optimized glycemic control in type 1 diabetes, smoking was not a significant risk factor for macrovascular complications [9, 10]. The subjects participating in this study were young, and, thus, the DCCT was not optimally designed to study the role of tobacco use in macrovascular complications [9, 10]. Other studies in slightly older type 1 subjects with diabetes have shown that smoking does increase the risk for CHD. In type 2 subjects with diabetes, the UKPDS clearly showed that cigarette smoking is a significant and independent risk factor for CHD, stroke, as well as peripheral vascular disease [11]. In the Nurses' Health Study, in women with type 2 diabetes, it was demonstrated that smoking was associated in a dose-dependent manner with an increased mortality and CHD. The risk for mortality from all causes was 1.64 in diabetic women who smoked 15 to 34 cigarettes per day and 2.19 in women who smoked more than 34 cigarettes per day [12]. Ten years after having stopped smoking, the risk for mortality has normalized when compared with nonsmoking diabetic women. Another data has shown that compared with never-smokers, the relative risks for CHD were 1.66 for current smokers of 1 to 14 cigarettes per day and 2.68 for current smokers of 15 or more cigarettes per day [12].

A meta-analysis in the Asia-Pacific region, in men with diabetes, the hazard ratio for CHD comparing current smokers with nonsmokers was 1.42 [13]. Cigarette cessation strategies can be beneficial in terms of reducing the burden of CVD in men with diabetes [14].

A large prospective study by Chaturvedi et al. studied the effects of smoking cessation on cardiovascular risk in diabetic patients [15]. Mortality risks in previous smokers with diabetes were compared with risks for subjects who have never smoked. All-cause mortality risks were around 50% higher for patients who stopped smoking during the past 1–9 years and 25% higher in individuals who quit smoking before that, when compared with subjects who have never smoked [15]. The results from this study show that stopping smoking reduces mortality risk in diabetes, but risks still remain high several years after quitting smoking. The mortality risk with smoking in diabetes is dependent on the duration of smoking.

Smoking and Cerebrovascular Accident/ Stroke

Smoking also increases the risk of stroke in patients with diabetes, but the association may not be as strong as CHD. Smoking and HbA1c are predictors of stroke among the type 2 diabetes patients without a history of a previous stroke. In the London cohort of the 8-year prospective World Health Organization Multinational Study of Vascular Disease in Diabetes, it was shown that smoking was not significantly associated with stroke [16]. In a study using the general practice research database in the United Kingdom, smoking was an additional risk factor for stroke in type 2 diabetes patients [17]. In the Nurses' Health Study, in smokers who smoked 1 to 14 cigarettes per day, the risk was significant for CHD but not for stroke [12]. In those who smoked 15 cigarettes or more per day, the relative risks for CHD and stroke were 2.68 and 1.84, respectively [12]. Similar trends were shown in a Swedish study, in which the relative risk of smoking was higher in myocardial infarction (2.33) than for stroke (1.12) in 30- to 59-year-old patients [18].

Smoking cessation should be a main target for the prevention of CVDs in patients with type 2 diabetes and is also very cost-effective. Smoking cessation should be integrated in a multiple-risk-factor control program [19]. This was shown in the Steno-2 trial, where a decrease in smoking rate was combined with a successful decrease in other risk factors in the intensively treated group [20].

Smoking and Peripheral Artery Disease

Smoking is associated with exacerbation of peripheral artery disease in diabetes. Smoking per se is a risk factor for peripheral artery disease (Buerger's disease). The peripheral artery disease associated with smoking per se primarily affects the medium-sized arteries. In contrast, diabetes per se affects the more distal arteries and arterioles. The presence of smoking in the background of diabetes has a synergistic effect on the peripheral artery disease occurrence and progression [21]. Smoking at least one pack of cigarettes per day ([OR] 2.5; 95% CI 1.1, 6.0) was associated with a

significant increase in the occurrence of symptomatic peripheral artery disease [22]. The presence of diabetes was the strongest predictor of peripheral artery disease in smokers in that study [22]. Ankle brachial index (ABI) assessment has an important role in disease severity assessment as well as prognostication (predicting cardiovascular and all-cause mortality) [21].

Smoking Cessation, Diabetes, and Technology

One of the aims of the comprehensive management plan for diabetes is to include smoking cessation plan for the patients with support from the family, friends, diabetic educator. and physician. The "5 A's"—ask, assess, advise, assist, and arrange—are five intervention steps suggested to help patients quit smoking (Box 43.1). Also, interventions to prevent relapse should be undertaken with patients who have quit smoking. Counseling and behavior therapy remain most important in helping patients quit smoking. Pharmacotherapy is often helpful with the use of nicotine replacement therapy (including nicotine patches, gum, and lozenges) and sustained-release bupropion. Patients receiving bupropion must be closely monitored for seizures and hyperglycemia. There is evidence supporting the safety and efficacy of varenicline in smokers with diabetes. However, the glycemic status must be monitored carefully in patients receiving varenicline as case reports of severe hypoglycemia in patients with type 1 diabetes exist. A meta-analysis reported that delivering structured smoking cessation interventions or medication for smoking cessation was found to have significantly better smoking abstinence rates compared to counselling or optional medication.

Box 43.1 Five Intervention Steps to Help Patients Quit Smoking

Ask: Identify active smoker/ex-smoker at each visit.
Assess: Determine person's willingness to quit smoking.
Advise: Strongly advise all tobacco users to quit.
Assist: Assist patients in quitting smoking.
Arrange: Arrange follow-up visits.

It must be highlighted that the weight gain and the associated transient mild increase in the risk of diabetes in patients who quit smoking should not be a deterrent for stopping smoking. It must be clearly highlighted to the smokers that quitting overall has a beneficial effect of quality of life and survival. In a large community-based cohort (Framingham Offspring Study data collected from 1984 through 2011), smoking cessation was associated with a lower risk of coronary artery disease events among participants without diabetes, and weight gain that occurred following smoking cessation did not modify this association, which supports a net cardiovascular benefit of smoking cessation, despite subsequent weight gain [23].

The diagnosis and treatment of diabetes or any of its complication are potential "teachable moments" for smoking cessation as at the time of diagnosis, patients were found to have significantly higher motivation to quit.

Recent reports have suggested that the use of Internet and mobile phone-based technology (mHealth) can go a long way in promoting healthy lifestyle habits and institute positive feedback mechanism, which can help in smoking cessation as well as ensuring better glycemic control in patients with diabetes [24].

Multiple-Choice Questions

1. Which of the following is the correct statement regarding the relationship of smoking and glycemia?
   (a) Smoking is linked with increased incidence of diabetes.
   (b) Smoking is linked with increased severity of diabetes.
   (c) The risk of developing diabetes in smokers has been found to be dose dependent.
   (d) All of the above.
2. Smoking is associated most evidently with which microvascular complications in type 2 diabetes?
   (a) Retinopathy
   (b) Nephropathy
   (c) Neuropathy
   (d) Gastroparesis
3. Other than retinopathy, smoking has been implicated in the development and progression of which other ocular diseases?
   (a) Age-related macular degeneration
   (b) Glaucoma
   (c) Cataract
   (d) All of the above
4. Which of the following is a false statement regarding mortality risks in smokers with diabetes?
   (a) Remains high even several years even after quitting smoking
   (b) Dependent on duration of smoking
   (c) Increases only in type 2 diabetes persons, not in type 1 diabetes persons
   (d) Dose dependent
5. What parts are primarily affected by the peripheral artery disease associated with smoking per se?
   (a) Medium-sized arteries

(b) Distal arteries and arterioles
(c) Large arteries
(d) Capillaries

6. What parts are primarily affected by the peripheral artery disease associated with diabetes per se?
   (a) Medium-sized arteries
   (b) Distal arteries and arterioles
   (c) Large arteries
   (d) Capillaries
7. What pharmacological agents are helpful in quitting smoking?
   (a) Nicotine gums/patches
   (b) Sustained-release bupropion
   (c) Varenicline
   (d) All of the above
8. Varenicline use for smoking cessation in type 1 diabetes persons has been reported with which adverse event?
   (a) Hypoglycemia
   (b) Hyperglycemia
   (c) Hypokalemia
   (d) Hyponatremia
9. What might be associated with smoking cessation in short term?
   (a) Weight gain
   (b) Weight loss
   (c) Increased risk of diabetes
   (d) A and C
10. Which of the following statement is incorrect regarding cessation of smoking?
   (a) Smoking cessation may lead to transient increase in body weight.
   (b) Smoking cessation may be associated with transient mild increase in the risk of diabetes.
   (c) Smoking cessation may lead to transient increased risk of coronary artery disease.
   (d) B and C.

Answers

1. Option D
2. Option B
3. Option D
4. Option C
5. Option A
6. Option B
7. Option D
8. Option A
9. Option D
10. Option C

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Part VIII

Acute Complications

Hyperglycemic Crises: Diabetic Ketoacidosis

44

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Diabetic ketoacidosis (DKA) most often occurs in patients with type 1 diabetes, but many patients with type 2 diabetes may develop ketoacidosis under stressful medical and surgical conditions [1]. In contrast to popular belief, DKA is more common in adults than in children. Data from the T1D Exchange Clinic Network including 2561 patients shows that young adults (18–25 years) have the highest occurrence of DKA (~5%) defined as ≥1 event in the prior 3 months [2]. In community-based studies [1, 2], more than 40% of patients with DKA are older than 40 years, and more than 20% are older than 55 years. Worldwide, infection is the most common precipitating cause for DKA, occurring in 30–50% of cases. Other precipitating causes are intercurrent illnesses (i.e., surgery, trauma, myocardial ischemia, pancreatitis), psychological stress, and noncompliance with insulin therapy.

Treatment of patients with DKA and hyperosmolar hyperglycemic syndrome (HHS) is associated with substantial mortality and healthcare costs. DKA is the leading cause of mortality among children and young adults with T1D, accounting for ~50% of all deaths in diabetic patients younger than 24 years of age [3]. In the United States, the overall inpatient DKA mortality is <1% [3, 4], but a higher rate is reported among elderly patients with life-threatening illnesses [3–6]. Mortality increases substantially with aging, with mortality rates for those over 65–75 years reaching 20–40%. The cause of death in patients with DKA rarely results from the metabolic complications of hyperglycemia or metabolic acidosis but relates to the underlying medical illness (i.e., trauma, infection) that precipitated the ketoacidosis.

In up to 25% of patients, the initial presentation consists of combined features of DKA and HHS. Over 30% of patients have features of both DKA and HHS with most recent evidence confirming that about one out of four patients will have both conditions at the time of presentation with hyperglycemic crisis [7]. Patients presenting with this phenotype have shown to have a worse prognosis and have a higher risk of mortality (8%) compared to those with isolated hyperglycemic crises (3% for isolated DKA and 5% for isolated HHS) [8].

Pathogenesis

DKA is characterized by uncontrolled hyperglycemia, metabolic acidosis, and increased circulating total body ketone concentration. Ketoacidosis results from the lack of, or ineffectiveness of, insulin with concomitant elevation of counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) [9, 10]. In individuals with and without diabetes, insulin controls hepatic glucose production by suppressing hepatic gluconeogenesis and glycogenolysis. In insulin-sensitive tissues such as muscle, insulin promotes protein anabolism, glucose uptake, and glycogen synthesis and inhibits glycogenolysis and protein breakdown. In addition, insulin inhibits lipolysis, ketogenesis, and free fatty acid (FFA) [1, 10]. In contrast, counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) promote metabolic pathways opposite to insulin action, both in the liver and peripheral tissues, leading to altered glucose production and disposal and increased lipolysis and the production of ketone bodies.

The pathophysiologic basis for hyperglycemia and ketoacidosis in DKA is shown in Fig. 44.1 [11]. Hyperglycemia results from increased hepatic glucose production and impaired glucose utilization in peripheral tissues. Increased gluconeogenesis results from the high availability of gluco-

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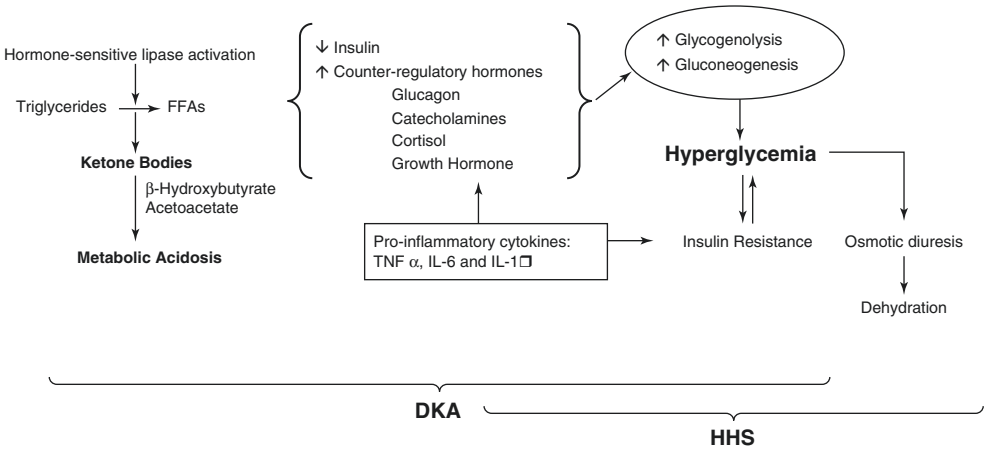

Fig. 44.1 Pathogenesis of hyperglycemic emergencies [11]. Hyperglycemia and the accumulation of ketone bodies result from a relative or absolute insulin deficiency and excess counter-regulatory hormones (glucagon, cortisol, catecholamines, and growth hormone). *Increased ketone bodies and ketoacidosis*. Decrease in insulin levels combined with increase in counter-regulatory hormones, particularly epinephrine, causes the activation of hormone-sensitive lipase in adipose tissue and breakdown of triglyceride into glycerol and free fatty acids (FFAs). In the liver, FFAs are oxidized to ketone bodies, a process predominantly stimulated by glucagon. The two major ketone bodies are β-hydroxybutyrate and acetoacetic acid. Accumulation of ketone bodies leads to a decrease in serum bicarbonate concentration and metabolic acidosis. Higher insulin levels present in HHS inhibit ketogenesis and limit metabolic acidosis. *Increased glucose production in DKA and HHS*. When insulin is deficient, hyperglycemia develops because of three processes: increased gluconeogenesis, accelerated glycogenolysis, and impaired glucose utilization by peripheral tissues. Hyperglycemia causes osmotic diuresis that leads to hypovolemia, decreased glomerular filtration rate, and worsening hyperglycemia

neogenic precursors (alanine, lactate, and glycerol) and from the increased activity of gluconeogenic enzymes (phosphoenolpyruvate carboxykinase (PEPCK), fructose-1,6-bisphosphatase, and pyruvate carboxylase) [10]. In addition, both hyperglycemia and high ketone levels cause an osmotic diuresis leading to hypovolemia and decreased glomerular filtration rate; the latter further aggravates hyperglycemia [11].

The mechanisms that underlie the increased production of ketones have been recently discussed in several reviews [1, 11]. The association of insulin deficiency and increased concentration of catecholamine, cortisol, and growth hormone causes the activation of hormone-sensitive lipase in adipose tissue. This enzyme causes endogenous triglyceride breakdown with subsequent release of large amounts of fatty acids into the circulation. Elevated FFAs are transported into the hepatic mitochondria, where they are oxidized to ketone bodies, a process predominantly stimulated by glucagon. Glucagon lowers the hepatic levels of malonyl coenzyme A (CoA), the first committed intermediate in the synthesis of long-chain fatty acids (lipogenesis) and a potent inhibitor of fatty acid oxidation. Malonyl CoA inhibits carnitine palmitoyl acyltransferase (CPTI), an enzyme that regulates the movement of FFA into the mitochondria. Therefore, reduction in malonyl CoA leads to stimulation of CPTI and effectively increases ketoacid production. In addition to increased ketone body production, there is also evidence that decreased clearance of ketoacids also contributes to the development of DKA.

Precipitating Causes

DKA is the initial manifestation of diabetes in 20–30% of patients with type 1 diabetes. In known diabetic patients, precipitating factors for DKA include infections, intercurrent illnesses, psychological stress, and noncompliance with therapy (Table 44.1). Infection is the most common precipitating factor for DKA, occurring in 30–50% of cases [1]. Urinary tract infection and pneumonia account for most infections. Other acute conditions that may precipitate DKA include cerebrovascular accident, alcohol abuse, pancreatitis, pulmonary embolism, myocardial infarction, and trauma. Drugs that affect carbohydrate metabolism such as corticosteroids, thiazides, and sympathomimetic agents may also precipitate the development of DKA.

One large retrospective review from the UK reported that hyperglycemic emergencies occurred at a rate of 1–2 per 1000 person-years following initiation of antipsychotics [13]. Of the antipsychotics, olanzapine and risperidone were associated with the highest risk [13]. Anticancer medications including immune checkpoint inhibitors such as ipilimumab, nivolumab, and pembrolizumab have been associated with newly diagnosed diabetes and DKA. Around 1% of patients taking these medications develop diabetes with half of them presenting with DKA as the first manifestation of diabetes. Patients with beta-cell autoimmunity are more susceptible to develop diabetes while taking anticancer medications [14–16].

Recently, the use of sodium glucose co-transporter 2 (SGLT2) inhibitors, a new class of oral antidiabetic agents that

Table 44.1 Causes of DKA and HHS

	% of admissions	
Precipitating cause	DKA[a]	HHS[b]
Infection	30–35	40–60
Failure to take insulin	15–40	0–35
New onset diabetes	20–25	20–25
Medical illnesses	10–20	10–15
Unknown	2–10	–

[a]Data are from refs. 2, 7, 12
[b]Data are from refs. 2, 7, 11

lowers plasma glucose by inhibiting proximal tubular reabsorption of glucose in the kidney, has been associated with DKA in patients with T1D and T2D [17–21]. An atypical presentation of DKA, which can lead to delayed recognition and treatment, has been referred to as "euglycemic DKA" due to only mild to moderate elevations in blood glucose reported in many cases. Compiled data from randomized studies with the use of SGLT2 inhibitors reported a very low incidence of DKA in patients with T2D (~0.07%) [22, 23]; however, the risk of ketosis and DKA is higher in patients with T1D. About 10% of patients with T1D treated with SGLT2 inhibitors develop ketosis, and 5% require hospital admission for DKA. Potential mechanisms have been proposed, including higher glucagon levels, reduction of daily insulin requirement leading to a decrease in the suppression of lipolysis and ketogenesis, and decreased urinary excretion of ketones [1].

The importance of noncompliance and psychological factors in the incidence of DKA has been emphasized in recent studies [24–26]. In a survey of 341 female patients with type 1 diabetes, Polonsky et al. reported that psychological problems complicated by eating disorders were a contributing factor in 20% of recurrent ketoacidosis in young women. In addition, eating disorders are reported in up to one-third of young women with type 1 diabetes. Factors that may lead to insulin omission in young subjects included fear of gaining weight with good metabolic control, fear of hypoglycemia, rebellion from authority, and diabetes-related stress. Lack of insulin treatment adherence is reported as a major precipitating cause for DKA in urban black and medically indigent patients. Many studies have reported that in urban black patients, poor compliance with insulin accounted for more than 50% of DKA cases admitted to a major urban hospital [1, 27]. Limited resources and lack of health insurance increase hospitalization rates for DKA by two- to threefold higher than comparable rates among diabetic persons with private insurance.

Although the use of continuous subcutaneous insulin infusion by an insulin pump was associated with an increased risk of DKA, recent mechanical improvements in such devices and the use of frequent home glucose monitoring have reduced this complication considerably [1]. In one of the largest prospective studies for therapy and follow-up of type 1 diabetes, the Diabetes Control and Complications Trial, the incidence of DKA was quite low in patients treated with continuous insulin infusion devices.

Ketosis-Prone Diabetes

A growing number of ketoacidosis cases have been identified in adult individuals with clinical features of type 2 diabetes that are not accompanied by precipitating factors [28]. This variant of type 2 diabetes has been referred to as ketosis-prone diabetes [29]. Patients with ketosis-prone diabetes are usually obese, have a strong family history of diabetes, and have a low prevalence of autoimmune markers [28]. The age of onset of ketosis-prone diabetes is usually in the fourth or fifth decade of life; however, the incidence has been increasing in the pediatric population. The prevalence is two- to threefold higher in men compared to women. While this entity has been reported across different ethnicities worldwide, people of African origin and Hispanics appear to have the highest risk [30]. Most patients present with a few weeks of polyuria, polydipsia, and weight loss and are found to have severe hyperglycemia accompanied with urinary ketonuria or frank DKA [31]. The clinical course of patients with ketosis-prone diabetes is different than those with chronic insulin dependence from type 1 diabetes with DKA. Many obese subjects with ketosis-prone diabetes experience near-normoglycemic remission off insulin therapy within the first few months of treatment. While at the beginning, these patients show impairments in both insulin secretion and insulin action, aggressive diabetes management results in significant improvement in β-cell function and insulin sensitivity that is usually sufficient to allow discontinuation of insulin therapy in almost 70% of individuals within a few months of treatment [32, 33].

COVID-19 and DKA

With the recent coronavirus disease 2019 (COVID-19) pandemic, there is now accumulating evidence that suggests a higher frequency and severity of DKA among those with COVID-19. A higher number of DKA admissions occurred during the COVID-19 pandemic, which was mostly seen among those with type 2 diabetes and newly diagnosed diabetes and less frequently in patients with type 1 diabetes [12]. Possible reasons for this increased DKA incidence dur-

ing the pandemic include social restrictions, less access to medical care, and an increased prevalence in a sedentary lifestyle. Results from a large cohort of patients with DKA during the COVID-19 pandemic showed that patients with COVID-19 had a higher body mass index, higher insulin requirements, prolonged time to resolution of DKA, and a sixfold higher rate of mortality compared with patients without COVID-19 [34].

Diagnosis

Symptoms and Signs

Symptoms of hyperglycemia including polyuria, polydipsia, and weight loss are usually present for several days prior to the development of DKA [3, 11]. Two-thirds of patients present with weakness, nausea, vomiting, and abdominal pain [35]. Abdominal pain, sometimes mimicking an acute abdomen, is especially common in children; although the cause has not been elucidated, delayed gastric emptying and ileus induced by electrolyte disturbance and metabolic acidosis have been implicated as possible causes of abdominal pain.

Physical examination reveals signs of dehydration, including loss of skin turgor, dry mucous membranes, tachycardia, and hypotension. Mental status can vary from full alertness to profound lethargy; however, fewer than 20% of patients are hospitalized with loss of consciousness [10]. Acetone on breath and labored Kussmaul respiration may also be present on admission, particularly in patients with severe metabolic acidosis.

Laboratory Findings

The syndrome of DKA consists of the triad of hyperglycemia, ketosis, and acidemia (Table 44.2) [10]. Diagnostic criteria for DKA accepted by the American Diabetes Association are a blood glucose greater than 250 mg/dL, pH lower than 7.3, serum bicarbonate lower than 15 mEq/L, and a moderate degree of ketonemia (hydroxybutyrate and acetoacetic acid greater than 3 mmol) [3]. The key diagnostic feature is the elevation in circulating total blood ketone concentration.

Table 44.2 Diagnostic criteria for DKA

	DKA		
	Mild	Moderate	Severe
Plasma glucose (mg/dL)	>250	>250	>250
Arterial pH	7.25–7.30	7.00–<7.24	<7.00
Serum bicarbonate (mEq/L)	15–18	10–<15	<10
Urine ketone[a]	Positive	Positive	Positive
Serum ketone	Positive	Positive	Positive
Effective serum osmolality[b]	Variable	Variable	Variable mOsm/kg
Anion gap	>10	>12	>12
Alteration in sensorium	Alert	Alert/drowsy	Stupor/coma

Modified with permission from Diabetes Care from the American Diabetes Association Consensus Statement on Hyperglycemic Crises, 2009 [3]

[a] Nitroprusside reaction

[b] Effective serum osmolality: 2[measured Na^+ (mEq/L)] + glucose (mg/dL)/18

Table 44.3 Useful formulas for the evaluation of DKA

1. Calculation of anion gap (AG):
$$AG = [Na^+] - [Cl^- + HCO3^-]$$
2. Total and effective serum osmolality:
$$\text{Total} = 2[Na^+] + \frac{\text{glucose}(\text{mg/dL})}{18} + \frac{\text{BUN}(\text{mg/dL})}{2.8}$$
$$\text{Effective} = 2[Na^+] + \frac{\text{glucose}(\text{mg/dL})}{18}$$
3. Corrected serum sodium:
$$\text{Corrected [Na+]} = \frac{1.6 \times \text{glucose}(\text{mg/dL}) - 100}{100} + [\text{measured Na+}]$$
4. Total body water (TBW) deficit:
$$\text{TBW deficit} = [\text{wt (kg)} \times 0.6] - \left[\frac{\text{corrected } Na^+}{140}\right] - 1$$

Assessment of ketonemia can be performed by the nitroprusside reaction, which provides a semiquantitative estimation of acetoacetate and acetone levels, or by direct measurement of beta-hydroxybutyrate, the main ketoacid in DKA.

Accumulation of ketoacids results in an increased anion gap metabolic acidosis. The anion gap is calculated by subtracting the sum of chloride and bicarbonate from the sodium concentration [Na-(Cl + HCO_3)]. The normal anion gap is 12 ± 2 mEq/L (Table 44.3).

Not all patients who present with ketoacidosis have DKA. Patients with chronic ethanol abuse with a recent binge culminating in vomiting and acute starvation may develop alcoholic ketoacidosis (AKA). The key difference between AKA and DKA is the concentration of blood glucose. DKA is characterized by severe hyperglycemia; the presence of ketoacidosis without hyperglycemia in an alcoholic patient suggests AKA. In addition, some patients with decreased food intake lower than 500 calories/day may present with starvation ketosis. The diagnosis of starvation ketosis is suggested by a history of poor intake and the fact that it rarely presents with a serum bicarbonate concentration less than 18 mEq/L [10].

The following laboratory findings should be kept in mind in patients admitted with suspected or confirmed DKA. Leukocytosis is present in most patients with DKA; however, a leukocyte count greater than 25,000 mm^3 or the presence of greater than 10% neutrophil bands is seldom seen in the absence of bacterial infection [10]. The admission serum sodium is usually low because of the osmotic flux of water from the intracellular to the extracellular space in the presence of hyperglycemia. An increase in serum sodium concentration in the presence of hyperglycemia indicates a rather profound degree of water loss. To assess the severity of sodium and water deficit, serum sodium may be corrected by adding 1.6 mg/dL to the measured serum sodium for each 100 mg/dL of glucose above 100 mg/dL [36]. The admission serum potassium concentration is usually elevated in patients with DKA. These high levels occur because of a shift of potassium from the intracellular to the extracellular space due to acidemia, insulin deficiency, and hypertonicity.

Treatment

The American Diabetes Association algorithm for the management of hyperglycemic emergencies is shown in Fig. 44.2 [3]. Successful treatment of DKA requires frequent monitoring of patients, correction of hypovolemia and metabolic disorder, and careful search for the precipitating cause for DKA. Most patients with uncomplicated DKA can be treated in the emergency department or in step-down units, if close nursing supervision and monitoring are available. Several studies have failed to demonstrate clear benefits in treating DKA patients in the intensive care unit (ICU) compared to step-down units [37–39]. The mortality rate, length of hospital stay, and time to resolve ketoacidosis are similar between patients treated in ICU and non-ICU settings. In addition, ICU admission has been associated with more laboratory testing and higher hospitalization cost in patients with DKA [37, 40].

Patients with mild to moderate DKA can be safely managed in the emergency department or in step-down units, and only patients with severe DKA or those with a critical illness as precipitating cause (i.e., myocardial infarction, gastrointestinal bleeding, sepsis) [3, 41] should be treated in the ICU. Patients with altered mental status and comatose state have higher mortality than alert patients and should be managed in the ICU.

Fluid Therapy

All patients with DKA are volume depleted (fluid deficit ~5–8 L) requiring aggressive fluid resuscitation to restore intravascular volume and renal perfusion. Isotonic saline (0.9% NaCl) is infused at a rate of 500–1000 mL/h during the first 2 h, but larger volume may be required in patients with hypovolemic shock to restore normal blood pressure and tissue perfusion. After intravascular volume depletion has been corrected, the rate of normal saline infusion should be reduced to 250 mL/h or changed to 0.45% saline depending upon the serum sodium concentration. The free water deficit can be estimated, based on corrected serum sodium concentration, using the following equation: water deficit = (0.6)(body weight in kilograms) × (1 − [corrected sodium/140]) [10]. The goal is to replace half the estimated water deficit over a period of 12–24 h.

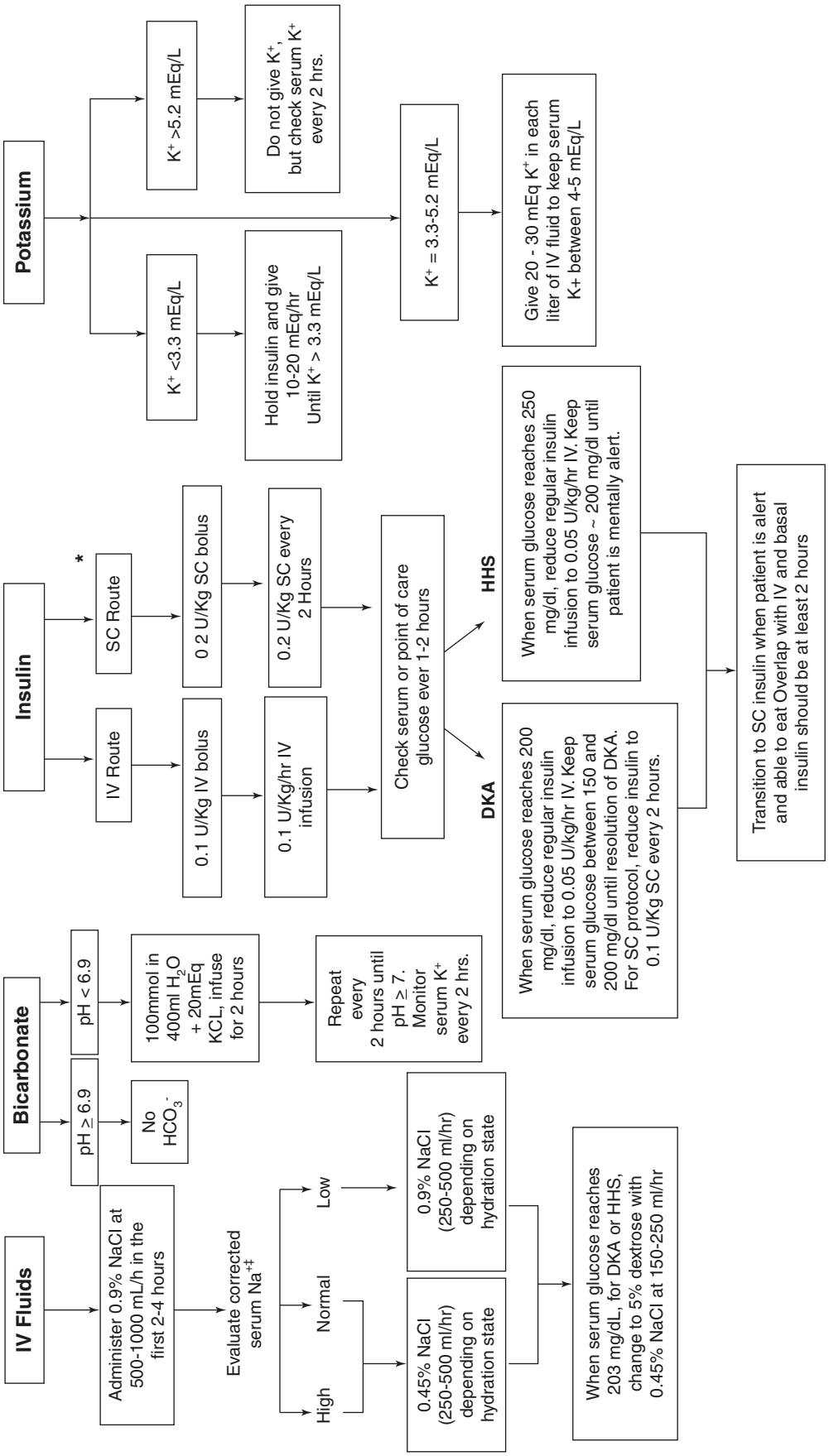

Fig. 44.2 Management of hyperglycemic emergencies [3]. *Subcutaneous Insulin Protocol has not been validated for HHS (Modified with permission from Diabetes Care from the American Diabetes Association Consensus Statement on Hyperglycemic Crises, 2009 [3])

Once the plasma glucose reaches 250 mg/dL, replacement fluids should contain 5–10% dextrose to allow continued insulin administration until ketonemia is controlled while avoiding hypoglycemia [3]. An important aspect of fluid management in patients with DKA is to replace the volume of urinary losses. Failure to adjust fluid replacement for urinary losses may delay the correction of electrolytes and water deficit.

Capillary blood glucose testing should be determined during treatment every 1–2 h at the bedside using a glucose oxidase reagent strip; and blood should be drawn every 4 h for determination of serum electrolytes, glucose, blood urea nitrogen, creatinine, magnesium, phosphorus, and venous pH until resolution of ketoacidosis.

Insulin Therapy

Insulin therapy is the cornerstone of DKA management. Insulin lowers blood glucose concentration by increasing peripheral glucose utilization and reducing hepatic glucose production. In addition, insulin therapy inhibits lipolysis and the release of free fatty acid from adipose tissue and decreases ketogenesis.

Regular insulin given intravenously by continuous infusion remains the drug of choice. Intermittent infusion or hourly boluses of low-dose intravenous insulin should be avoided because of regular insulin's [3] short half-life. The American Diabetes Association recommends an initial intravenous bolus of regular insulin of 0.1 units/kg of body weight, followed by a continuous infusion of regular insulin at a dose of 0.1 units/kg per hour until blood glucose levels reach 250 mg/dL [1]. Once glucose is lower than 250 mg/dL, dextrose should be added to intravenous fluids, and the insulin infusion rate is reduced to 0.05 units/kg per hour. Thereafter, the rate of insulin administration should be adjusted to maintain glucose levels at approximately 150–200 mg/dL and continued until ketoacidosis is resolved. Resolution of hyperglycemia takes about 4–6 h, but resolution of ketoacidosis takes longer (~10–14 h); thus, dextrose is needed to allow insulin infusion and the prevention of hypoglycemia [10].

Several studies and a meta-analysis have reported that the administration of hourly or every 2 h doses of subcutaneous rapid-insulin analogs (lispro and aspart) represents an effective alternative to the intravenous infusion of regular insulin [42–44]. The administration of an insulin subcutaneous bolus of 0.2–0.3 U/kg followed by 0.1–0.2 U/kg every 1–2 h, respectively, until glucose is <250 mg/dL. The dose is then reduced by half to 0.05 U/kg every 1 h or 0.01 U/kg every 2 h until resolution of DKA [42, 45]. Using scheduled subcutaneous insulin allows for safe and effective treatment in the emergency room and step-down units without the need for ICU care in patients with mild or moderate DKA. The use of intramuscular injections of rapid-acting insulin is also effective in the treatment of DKA, but this route tends to be more painful than subcutaneous injection and might increase the risk of bleeding among patients receiving anticoagulation therapy [1, 46]. The use of rapid-acting subcutaneous insulin analogs is not recommended for patients with severe and complicated DKA.

Potassium

An estimated total body potassium deficit of ~3–5 mEq/kg of body weight has been reported in adult patients with DKA [10]; however, most patients present with normal or high serum potassium. With initiation of insulin and fluid therapy, the extracellular potassium concentration invariable falls. Insulin therapy and correction of acidosis decrease serum potassium levels by stimulating cellular potassium uptake in peripheral tissues. Therefore, all patients require intravenous potassium to prevent hypokalemia.

The American Diabetes Association recommends the administration of intravenous potassium chloride (20–30 mEq/L) as soon as the serum potassium concentration is below 5.5 mEq/L. The treatment goal is to maintain serum potassium levels within the normal range of 4–5 mEq/L. A presentation with severe hypokalemia may be aggravated during insulin administration, which can induce life-threatening arrhythmias and respiratory muscle weakness. Thus, if the initial serum potassium is equal or lower than 3.0 mEq/L, potassium replacement should be given for 1–2 h at a rate of 10–20 mEq per hour, before insulin infusion is started.

Bicarbonate

Bicarbonate administration in patients with DKA is rarely indicated. Several controlled studies have failed to show any benefit from bicarbonate therapy in patients with DKA and arterial pH between 6.9 and 7.1 [3, 10]. Despite the lack of evidence, most experts in the field recommend that in patients with severe metabolic acidosis (pH < 6.9–7.0), 44.6 mEq of sodium bicarbonate should be added to a liter of hypotonic saline until pH rises to at least 7.0. In patients with arterial pH ≥ 7.0, no bicarbonate therapy is necessary.

Phosphate

Total body phosphate deficiency is present in most patients with DKA. Similar to studies with bicarbonate replacement, several studies have failed to show any beneficial effect of phosphate replacement on clinical outcome [3, 10]. Aggressive phosphate therapy may be potentially hazardous, as indicated in case reports of children with DKA who developed hypocalcemia and tetany secondary to intravenous phosphate administration. Careful phosphate replacement may be indicated in patients with cardiac dysfunction, anemia, respiratory depression, and in those with serum phosphate concentration lower than 1.0–1.5 mg/dL. If phosphate replacement is needed, it should be administered as a potassium salt, by giving half as potassium phosphate and half as potassium chloride. In such patients, because of the risk of hypocalcemia, serum calcium and phosphate levels must be monitored during phosphate infusion.

Transition to Subcutaneous Insulin

Patients with DKA should be treated with continuous intravenous or frequent subcutaneous insulin administration until ketoacidosis is resolved. Criteria for resolution of DKA include a blood glucose lower than 200 mg/dL, a serum bicarbonate level equal to or greater than 18 mEq/L, a venous pH greater than 7.3, and a calculated anion gap equal to or lower than 14 mEq/L [3, 10].

The half-life of insulin is <10 min [47]; thus, abrupt cessation of the insulin may result in rebound hyperglycemia, ketogenesis, and recurrent metabolic acidosis. Subcutaneous insulin should be given at least 2 h before discontinuing the intravenous insulin infusion [3]. The initial dose of NPH should be given 2 h before stopping insulin infusion. Earlier initiation 3–4 h before discontinuation of insulin drip should be considered when using basal insulin analogs (glargine, detemir, degludec), which have a longer delay in onset of action than NPH insulin. One randomized controlled trial evaluated the effect of co-administration of IV insulin with subcutaneous glargine shortly after the onset of treatment of DKA compared to IV insulin alone [48]. Patients who received glargine had slightly shorter time to resolution of DKA and shorter hospital stay; however, these differences were not statistically significant [48]. Another study found that the administration of basal insulin analogs early during treatment (more than 4 h) could reduce the frequency of rebound hyperglycemia after transition off insulin drip [49].

Patients with known diabetes may be given insulin at the dosage they were receiving before the onset of DKA. In patients with newly diagnosed diabetes, an initial insulin total insulin dose of 0.6 units/kg/day is usually sufficient to achieve and maintain metabolic control.

The use of insulin analogs in a basal-bolus regimen is the preferred insulin regimen and has been shown to reduce the risk of hypoglycemia compared to human insulin (NPH and regular) regimen [50]. If insulin analogs are used, the total daily dose is given 50% as basal (glargine, detemir, degludec) once daily at the same time of the day and 50% as prandial insulin 150–15 min before meals. If a patient is to be treated with NPH/regular insulin combination, the total daily dose should be given two-thirds in the morning and one-third in the evening as a split-mixed dose consisting of two-thirds of NPH and one-third of regular insulin.

Prevention

Patient education and the implementation of protocols aiming to acute and maintenance insulin administration after discharge may reduce lapses in treatment and are cost-effective ways to reduce the future risk of hospitalization for hyperglycemic emergencies [11]. Systems-based methods to reduce preventable causes of hyperglycemic emergencies may represent an important next step in reducing costs and improving patient care.

The frequency of hospitalizations for DKA has been reduced following diabetes education programs, improved follow-up care, and access to medical advice. The alarming frequency of insulin discontinuation due to economic reasons as the precipitating cause for DKA in low economic populations illustrates the need for health care legislation for reimbursement for medications to treat diabetes.

Home blood ketone monitoring, which measures beta-hydroxybutyrate levels on a fingerstick blood specimen, is commercially available ketones. Clinical studies have shown that elevation of beta-hydroxybutyrate levels is common in patients with poorly controlled diabetes and may allow early recognition of impending ketoacidosis, which may help to guide insulin therapy at home, and, possibly, may prevent hospitalization for DKA.

Multiple Choice Questions

1. Triad that is characteristic of diabetic ketoacidosis:
   (a) *Hyperglycemia, ketosis, and acidemia*.
   (b) Frequent urination, thirst, hunger.
   (c) Hyperglycemia, weight loss, fatigue.
   (d) High levels of hyperglycemia, dehydration, hyper-osmolality.
   (e) Hyperglycemia, depression of alert, unresponsiveness.
2. The key diagnostic feature of diabetic ketoacidosis:
   (a) Hyperglycemia.
   (b) Dehydration.
   (c) Confusion, stupor, and coma.
   (d) Polyuria.

(e) *Ketonemia*.

3. Which is the most common precipitating cause for diabetic ketoacidosis?
   (a) Insufficient insulin dose.
   (b) *Infection*.
   (c) Excessive food intake.
   (d) Psychological stress.
   (e) Noncompliance with therapy.
4. Ketoacidosis results from:
   (a) *Lack of or ineffectiveness of insulin and elevation of counter-regulatory hormones*.
   (b) Accelerated immune attack on beta-cells.
   (c) Increasing demands of insulin.
   (d) Low C-peptide levels.
   (e) Low compliance of patients.
5. Antidiabetic agents associated with diabetic ketoacidosis:
   (a) Metformin.
   (b) Sulfonylureas.
   (c) Glitazones.
   (d) DPP-4 inhibitors.
   (e) *SGLT2 inhibitors*.
6. Clinical symptoms of diabetic ketoacidosis include:
   (a) *Polyuria.*
   (b) *Polydipsia.*
   (c) *Weight loss.*
   (d) *Abdominal pain.*
   (e) *Labored Kussmaul respiration.*
7. The requirements for the successful treatment of diabetic ketoacidosis include:
   (a) Frequent monitoring.
   (b) Rehydration.
   (c) Insulin.
   (d) Investigating and correcting the cause.
   (e) *All of the above*.
8. The correct formula to estimate corrected serum sodium:

   (a) Corrected [Na+] = $\frac{6.1 \times \text{glucose}(\text{mg/dL}) + 100}{100}$ + [measured Na+].

   (b) Corrected [Na+] = $\frac{6.1 \times \text{glucose}(\text{mg/dL}) - 100}{100}$ + [measured Na+].

   (c) *Corrected [Na+]* = $\frac{1.6 \times \textit{glucose}(\textit{mg/dL}) - 100}{100}$ + *[measured Na+].*

   (d) Corrected [Na+] = $\frac{1.5 \times \text{glucose}(\text{mg/dL}) + 100}{100}$ + [measured Na+].

   (e) Corrected [Na+] = $\frac{6.1 \times \text{glucose}(\text{mg/dL}) + 200}{100}$ + [measured Na+].

9. Regarding insulin therapy, the American Diabetes Association recommends:
   (a) *An initial intravenous bolus of regular insulin of 0.1 units/kg of body weight, followed by a continuous infusion of regular insulin at a dose of 0.1 units/kg per hour until blood glucose levels reach 250 mg/dL.*
   (b) An initial intravenous bolus of intermediate-acting insulin of 0.1 units/kg of body weight, followed by a continuous infusion of long-acting insulin at a dose of 0.1 units/kg per hour until blood glucose levels reach 250 mg/dL.
   (c) An initial intravenous bolus of regular insulin of 1 units/kg of body weight, followed by a continuous infusion of regular insulin at a dose of 1 units/kg per hour until blood glucose levels reach 100 mg/dL.
   (d) An initial intravenous bolus of regular insulin of 10 units, followed by a continuous infusion of regular insulin at a dose of 1 units/kg per hour until blood glucose levels reach 150 mg/dL.
   (e) An initial intravenous bolus of insulin lispro of 1 units/kg of body weight, followed by a continuous infusion of regular insulin at a dose of 1 units/kg per hour until blood glucose levels reach 250 mg/dL.
10. Criteria for resolution of diabetic ketoacidosis include:
   (a) Blood glucose lower than 300 mg/dL, a serum bicarbonate level equal to or greater than 18 mEq/L, a venous pH greater than 3.7, and a calculated anion gap equal to or lower than 41 mEq/L.
   (b) *A blood glucose lower than 200 mg/dL, a serum bicarbonate level equal to or greater than 18 mEq/L, a venous pH greater than 7.3, and a calculated anion gap equal to or lower than 14 mEq/L.*
   (c) A blood glucose lower than 200 mg/dL, a serum bicarbonate level equal to or greater than 18 mEq/L, a venous pH greater than 7.4, and a calculated anion gap equal to or lower than 14 mEq/L.
   (d) A blood glucose lower than 150 mg/dL, a serum bicarbonate level equal to or greater than 18 mEq/L, a venous pH greater than 7.4, and a calculated anion gap equal to or lower than 14 mEq/L.
   (e) A blood glucose lower than 120 mg/dL, a serum bicarbonate level equal to or greater than 18 mEq/L, a venous pH greater than 7.4, and a calculated anion gap equal to or lower than 14 mEq/L.

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Hypoglycemia: Diagnosis, Management, and Prevention

45

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Objectives

To know:

- The definition and classification of hypoglycemia
- The normal physiologic counterregulatory response to hypoglycemia and glycemic thresholds
- The altered counterregulatory responses to hypoglycemia
  - T1D
  - Long-standing T2D
  - Hypoglycemia unawareness
  - Hypoglycemia-associated autonomic failure
- The epidemiology of hypoglycemia
- The detection, diagnosis, and causes of hypoglycemia
- The risk factors of hypoglycemia
- The treatment of hypoglycemia
- The strategies to reduce or prevent hypoglycemia
- The technology in the reduction and prevention of hypoglycemia
- Beta cell replacement for the treatment of severe hypoglycemia

Introduction

Hypoglycemia is one of the most important barriers to achieve optimal glycemic management in the treatment of diabetes. It may cause potentially incapacitating and life-threatening events in patients with type 1 diabetes (T1D) and long-standing type 2 diabetes (T2D). It precludes patients from reaching euglycemia, limiting the benefits of tight control. Patients may develop unawareness of hypoglycemic symptoms due to blunted responses resulting from recurrent episodes of hypoglycemia posing them into grave danger.

Hypoglycemia Definition and Classification

The ADA (American Diabetes Association) defined hypoglycemia in patients with diabetes as "all episodes of abnormally low plasma glucose concentration that expose the individual to potential harm." The International Hypoglycemia Study Group, endorsed by the ADA, and the European Association for the Study of Diabetes define hypoglycemia in three levels (Table 45.1) [1, 3, 4].

Level 1 Measurable glucose concentration of <70 mg/dL (3.9 mmol/L) or less but >54 mg/dL (3.0 mml/L). A blood glucose level concentration of 70 mg/dL has been recognized as a threshold for neuroendocrine response to falling glucose in people without diabetes. It is considered clinically important

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Table 45.1 Levels of hypoglycemia

Level	Description	Glycemic criteria	Description
1	Hypoglycemia alert	≤70 mg/dL	Sufficiently low for treatment with fast acting carbohydrates and dose adjustment of glucose-lowering therapy
2	Clinically relevant	≤54 mg/dL	Sufficiently low to indicate serious, clinically important hypoglycemia
3	Severe hypoglycemia		Hypoglycemia associated with severe impairment requiring external assistance for recovery

Adapted from [1, 2]

Table 45.2 Clinical classification of hypoglycemia in diabetes

Severe	Requiring assistance of another individual to administer carbohydrates, glucagon, or rescue therapy.
Symptomatic	Typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration <70 mg/dL (3.9 mmol/dL)
Asymptomatic	Not accompanied by typical symptoms of hypoglycemia but the measured plasma glucose is <70 mg/dL (3.9 mmol/dL)
Probable	Symptoms typical of hypoglycemia are present but a measured plasma glucose of <70 mg/dL (3.9 mmol/dL) could not be determined
Pseudo-hypoglycemia	A person reports symptoms of hypoglycemia, but the plasma glucose concentration is >70 mg/dL (3.9 mmol/dL)

Adapted from [4]

(independent of the severity of acute hypoglycemic symptoms) and requires attention to prevent hypoglycemia [2].

Level 2 Defined as a glucose concentration <54 mg/dL (3.0 mml/L), it indicates serious clinically important hypoglycemia. It is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycemic event. These low levels may lead to defective hormonal counterregulation and impaired awareness of hypoglycemia. This clinical scenario warrants investigation and review of the medical regimen.

Level 3 Defined as a severe event characterized by altered mental status and/or physical functioning that requires assistance from another person for recovery. A subgroup of severe hypoglycemia is *severe hypoglycemic coma*, which is described as a severe hypoglycemic event resulting in coma or convulsions requiring parenteral therapy [2, 5].

The clinical classification of hypoglycemia includes severe, symptomatic, asymptomatic, probable, and pseudo-hypoglycemia (Table 45.2).

Physiology of Hypoglycemia

Glucose is the predominant metabolic source of energy for the brain, as it requires a constant and adequate supply of glucose. Under normal post-absorptive conditions, the brain accounts for 65% of whole-body glucose. The brain cannot synthesize nor store glucose under normal physiologic conditions but can adapt and utilize other substrates. Thus, during periods of fasting, ketone bodies, lactate, and alanine can be used as alternative brain fuels [6, 7].

Decreased Glucose Uptake by the Brain

- When blood glucose drops to 65–70 mg/dL (3.6–3.0 mmol/L), brain glucose uptake falls.
- At 54 mg/dL (3.0 mmol/L), the blood-to-brain glucose transport becomes rate limiting for brain glucose metabolism [7].

Normal Glucose Counterregulation

In defense against declining plasma glucose concentrations, several physiological mechanisms have evolved to prevent and correct hypoglycemia [6].

First Defense

Inhibition of endogenous insulin secretion. Insulin is the principal physiological factor that lowers plasma glucose. Insulin is secreted primarily in response to glucose, but amino acids, non-esterified fatty acids, adrenergic stimulation, and acetylcholine can also activate its secretion. Insulin secretion can be inhibited by hypoglycemia, insulin itself, somatostatin, and adrenergic activity [7].

Secondary Defense

Increased glucagon release. Glucagon is released from the alpha cells in the islet of Langerhans. The factors that stimulate its release include hypoglycemia, amino acids, catecholamines (epinephrine and norepinephrine), and free fatty acids. Inhibition of glucagon release includes insulin and somatostatin. Glucagon's physiologic actions are restricted almost exclusively by the liver, stimulating a rapid increase in hepatic production over a period of 10–15 min. The initial rise in glucose output is provided by an increase in hepatic glycogenolysis. If hypoglycemia continues, glucagon can stimulate hepatic gluconeogenesis; this can only be done if there are three carbon precursors present (glycerol, lactate, amino acids) [7].

Third Defense

Increased release of epinephrine. Similar to glucagon, epinephrine can act rapidly to increase hepatic glucose output by stimulating glycogenolysis. If hypoglycemia continues and three carbon precursors are present, epinephrine will stimulate gluconeogenesis. Epinephrine also decreases glucose utilization by directly inhibiting tissue glucose uptake and by inhibiting insulin release. Epinephrine is approximately ten times more potent than norepinephrine in producing these effects. Epinephrine stimulates glucose production directly by a beta-adrenergic mechanism and indirectly by inhibiting insulin secretion by an alpha-adrenergic mechanism. Glucose counterregulation from insulin-induced hypoglycemia is primarily by glycogenolysis during the first 2 h by gluconeogenesis thereafter. While the effect of both glucagon and epinephrine on glucose production is transient, the effect of epinephrine to limit glucose utilization is sustained [7].

Late Defense

Release of cortisol and growth hormone. Increased secretion of cortisol and growth hormone is involved in defense against prolonged hypoglycemia. Both can increase glucose through increases in gluconeogenesis. Both hormones can also inhibit insulin-stimulated peripheral glucose uptake and can increase proteolysis and lipolysis. However, prolonged hypoglycemia (3–5 h) is needed before the metabolic effects are measurable, and even at that time, they only represent 20–25% of the action of epinephrine. Thus, cortisol and growth hormone are not critical to recovery from even prolonged hypoglycemia or to the prevention of hypoglycemia after an overnight fast [7, 8].

Key Points

- The release of neuroendocrine counterregulatory hormones and the inhibition of endogenous insulin secretion occur before a healthy adult can feel any symptoms of hypoglycemia.
- In the acute phase of hypoglycemia, there is an increase in the concentrations of glucagon and epinephrine (within minutes); increases of cortisol and growth hormone occur later.
- Glucagon plays a primary role in the prevention and correction of hypoglycemia. Epinephrine is not normally critical but becomes critical when glucagon is deficient.
- Insulin, glucagon, and epinephrine play a major role in the prevention and correction of hypoglycemia. All of these three factors are impaired in diabetes (Fig. 45.1).

Glycemic Thresholds

Glycemic thresholds for the activation of counterregulatory hormones have been reported to be at or just below the lower limit of normal plasma glucose range and elicit a characteristic sequence of response (Fig. 45.1) with a defined hierarchy. Symptoms are generated at blood glucose concentrations around 50–58 mg/dL in young adults [7].

Glycemic Mechanisms

Falling plasma glucose concentrations are detected by glucose-responsive neurons in the hypothalamus and other regions of the brain. There is evidence that glucose sensors in the periphery, apart from pancreatic beta cells, have been found in the intestine, hepato-portal vein, and carotid body. Within the central nervous system (CNS), studies have identified a number of areas that contain neurons sensitive to local changes in glucose. One brain region in particular, the VMH (ventromedial hypothalamus), appears to play a crucial role during hypoglycemia. The specialized glucose-sensing neurons in the CNS have been broadly defined as either glucose exited, which increase their action potential frequency when glucose rises, or glucose inhibited, which increase their action potential frequency when glucose levels fall. These neurons are liable to react in a coordinated manner to alterations in the glucose level to which they are exposed. The neurons also respond to other metabolites such as lactate and beta hydroxybutyrate, as well as hormones such as insulin, leptin, and possibly glucagon-like peptide 1, reflecting the central role they play in responding to alterations in fuel supply and in maintaining glucose homeostasis [9].

Pathophysiology of Glucose Counterregulation in Diabetes

T1D

The physiology of glucose counterregulation is extensively impaired in patients with T1D. As endogenous insulin secretion becomes completely deficient, the first physiologic line of defense (modulation of endogenous insulin) becomes lost. As the plasma glucose concentration falls, insulin levels do not decrease. In addition, the rise in glucagon secretion (second line of defense) is lost as glucose levels decline. This is an acquired defect, but it develops early in the course of T1D. Glucagon responses to other stimuli are intact; therefore, it cannot be attributed to alpha cells and must represent a signal abnormality. The deficient glu-

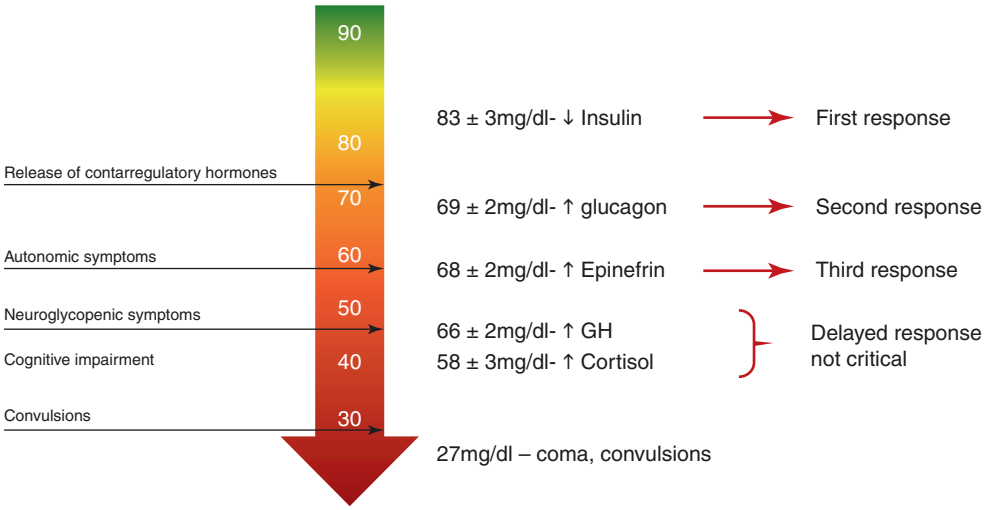


Fig. 45.1 Glycemic thresholds for hypoglycemia. (Adapted from [6–8])

cagon response is tightly related to absolute insulin deficiency. Insulin levels do not fall and glucagon levels do not rise as the plasma glucose concentration falls to hypoglycemic levels (Fig. 45.2).

The epinephrine response to failing glucose concentrations is commonly attenuated. This acquired abnormality is also selective in that epinephrine response to other stimuli is intact. However, while the deficient glucagon response to hypoglycemia appears to be absolute, the deficient epinephrine response appears to be a threshold abnormality. This epinephrine abnormality has been determined to be due to previous episodes of hypoglycemia [6].

Additional Facts

- Repeated hypoglycemia produces acute reductions (30–50%) in epinephrine, pancreatic polypeptide (a marker of parasympathetic nervous system activity), and muscle sympathetic nerve activity.
- Recent (within 24 h) antecedent hypoglycemia blunts the release of glucagon, growth hormone, adrenocorticotropic hormone (ACTH), and cortisol during subsequent hypoglycemia [7, 8].

T2D

The glucose counterregulatory mechanisms are generally intact during the initial course of T2D. Although there may be mild counterregulatory hormonal deficiencies, epinephrine secretion appears to be intact. Several studies have shown that counterregulatory hormonal release occurs at higher blood glucose levels in individuals with diabetes than in nondiabetic persons. This may confer greater protection against hypoglycemia. The glucagon response to hypoglycemia may be mildly decreased [10].

In many individuals with T2D who have insulin resistance, the lipolytic effects of epinephrine outweigh the effects of insulin on adipose tissue. Plasma free fatty acids increase in response to hypoglycemia in patients with T2D but not T1D. Epinephrine secretion in hypoglycemia may have a greater protective effect in insulin-resistant patients by promoting metabolic substrate release rather than storage. Epinephrine also stimulates the release of glucose from the kidney [10].

Nevertheless, as insulin progressively declines due to failing pancreatic endogenous secretion of insulin, glucagon response to hypoglycemia will progressively decline (Fig. 45.2).

It is important to consider the effects of aging in the response to hypoglycemia in patients with T2D as the majority of the population is elderly. With increasing age, the symptoms of hypoglycemia become less intense, and the symptom profile is modified. It has been reported that there is a modest attenuation of blood glucose recovery from hypoglycemia in the elderly nondiabetic population, in whom the rise of plasma epinephrine was slower than younger subjects. The elevation of glucagon and epinephrine occurred at lower plasma glucose levels in elderly nondiabetic patients compared to younger nondiabetic patients. The magnitude of the response is also lower in the elderly group. Also, the rate of insulin clearance from the circulation declines with increasing age, which may enhance the risk of hypoglycemia [10].

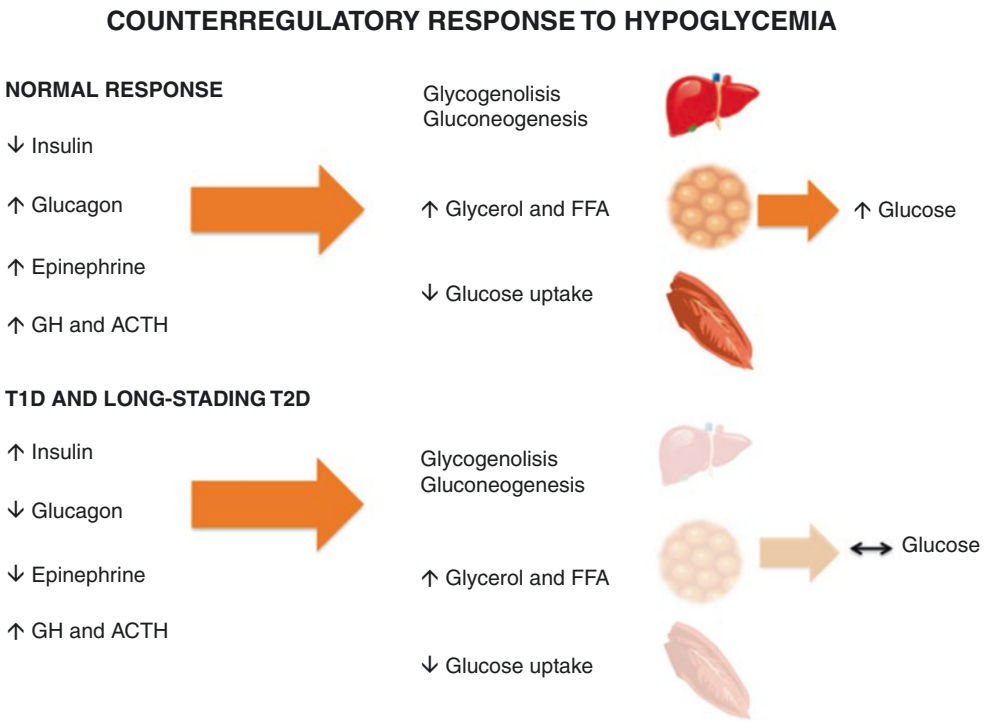


Fig. 45.2 Counterregulatory response to hypoglycemia

Hypoglycemia Unawareness

Individuals with intensive glucose control and multiple episodes of hypoglycemia find that activation of the physiologic responses to hypoglycemia is pushed to a lower plasma glucose level. This dangerous condition, called hypoglycemia unawareness, results in inability of patients to recognize falling plasma glucose until the value is <50 mg/dL (2.8 mmol/L). In some individuals, a falling plasma glucose level is not recognized at plasma glucose of 30 mg/dL (1.7 mmol/L). Thus, thresholds for the activation of physiologic defenses against hypoglycemia are labile and can change rapidly [7].

A major defect in the counterregulatory response to hypoglycemia in diabetes is a reduced autonomic response. Hypoglycemia unawareness occurs in 20% of patients with T1D and about half of the patients with long-standing T1D and is estimated to occur in about 25% of patients with long-standing T2D. As glucose declines, there is activation of the autonomic nervous system (ANS) that results in increased glucose production and decreased glucose uptake. The autonomic response is directly related to the generation of a symptomatic response to hypoglycemia. When this response becomes impaired, there is reduced awareness of the symptoms of hypoglycemia as well as reduced catecholamine release. The reduced autonomic response includes the sympathetic neural norepinephrine and acetylcholine, as well as the adrenomedullary epinephrine response (Fig. 45.3). As discussed previously, this reduced response becomes critical in patients with T1D and long-standing T2D, as there is no glucagon response, increasing the risk of hypoglycemia [9].

Key Points

- A defective autonomic response usually precedes prior episodes of hypoglycemia.
- This sets up a vicious cycle whereby hypoglycemia increases the likelihood of subsequent hypoglycemia.
- Hypoglycemia unawareness has been found to increase the frequency of hypoglycemia by a factor of 7 [7].

Hypoglycemia: Associated Autonomic Failure

The combination of defective glucose counterregulation (decreased glucagon release and attenuated epinephrine release) and hypoglycemia unawareness (reduced autonomic-sympathetic neural and adrenomedullary response) constitutes the clinical syndrome of hypoglycemia-associated autonomic failure (HAAF). It occurs in patients with T1D and long-standing T2D who have had recent antecedent hypoglycemia; it can also occur by sleep or prior exercise (Fig. 45.3) [11].

In patients with T1D, recent hypoglycemia has been shown to shift glycemic thresholds for autonomic and cognitive dysfunction responses to lower plasma glucose concentrations. It has been shown that avoidance of hypoglycemia

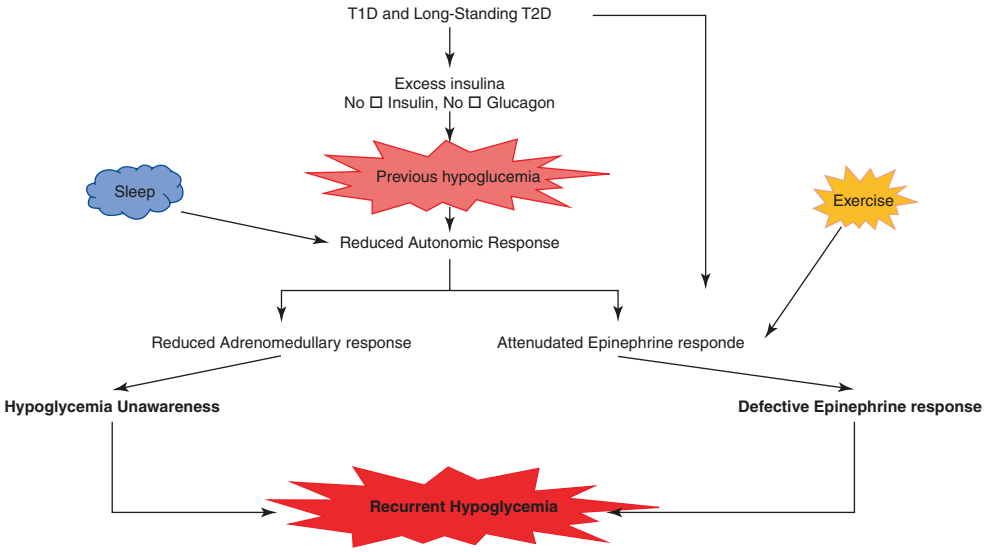


Fig. 45.3 Hypoglycemia-associated autonomic failure. (Adapted from [11])

for 2–3 weeks reverses hypoglycemia unawareness and improves the reduced epinephrine defective response; nevertheless, the glucagon response is not restored [8].

Additional Facts

- Repeated episodes of relative mild <70 mg/dL (3.9 mmol/L) and only brief durations (15–20 min) of hypoglycemia can independently blunt counterregulatory responses to subsequent hypoglycemia.
- One prolonged episode (2 h) of moderate hypoglycemia <50 mg/dL (2.8 mmol/L) is sufficient to induce HAAF within a few hours on the same day [7].

It has been proposed that repeated hypoglycemia increased cerebral glucose uptake in both healthy individuals and patients with T1D, thereby reducing the stimulus for neuroendocrine counterregulatory responses during subsequent hypoglycemia. Other mechanisms that have been proposed include activation of the hypothalamic-pituitary-adrenal axis, increases in neurotransmitters such as GABA, and changes in hypothalamic fuel sensors such as glucokinase or AMP kinase. Additionally, experimental evidence demonstrates that alcohol and opioids can downregulate subsequent ANS and neuroendocrine responses to hypoglycemia.

As mentioned above, sleep and exercise can induce HAAF. Compared to hypoglycemia during waking period, hypoglycemia during sleep (nocturnal hypoglycemia) elicits reduced counterregulatory response. Research has revealed a 60–70% reduction in epinephrine response during nocturnal hypoglycemia. Thus, exercise blunts ANS response (by 30–50%) to subsequent hypoglycemia and vice versa. This feed-forward vicious cycle of blunted ANS responses between exercise and hypoglycemia can occur after only a few hours and persists for at least 24 h following either stress [7].

Opioid receptor blockade, via treatment with naloxone, during hypoglycemia has been shown to prevent blunting responses (epinephrine and endogenous glucagon production) to next-day hypoglycemia in individuals with T1D [7].

Physiologic Stimuli to Blunted Hormonal Responses to Hypoglycemia

- Antecedent hypoglycemia
- Nocturnal hypoglycemia
- Sleep
- Alcohol
- Opioids [7]

Epidemiology

Iatrogenic hypoglycemia is more frequent in patients with profound endogenous insulin deficiency, T1D, and advanced T2D (as its incidence increases with the duration of diabetes). The frequency of hypoglycemia is about threefold greater in T1D than in T2D. Ninety percent of all patients who receive insulin have experienced hypoglycemic episodes [12].

During the Hypoglycemia Assessment Tool (HAT) global study, which was a non-interventional, multicenter, 6-month retrospective and 4-week prospective study involving 27,585 patients with either T1D or T2D treated with insulin, in 24 countries worldwide, it was found that during the prospective period, 83% of patients with T1D and 46.5% of patients with T2D reported hypoglycemia. Overall, there were 73.3

events/patient-year of hypoglycemia in T1D and 19.3 in patients with T2D. There were 11.3 events/patient-year of nocturnal hypoglycemia in T1D and 4.9 in T2D. And finally, there were 4.9 events/patient-year of severe hypoglycemia in T1D and 2.5 events/patient-year in T2D [13].

In the United States, from 1993 to 2005, around five million emergency department visits were due to hypoglycemic events, 25% of which led to hospitalization. This is especially common in elderly patients. Additionally, the NICE-SUGAR trial demonstrated that critically ill patients who are intensively controlled had an increased risk of moderate-to-severe hypoglycemia and increased risk of death [14].

A trial involving 33,675 hospitalized patients with and without diabetes found that hypoglycemia, with either insulin or spontaneous, was associated with increased short- and long-term mortality. In this cohort of hospitalized patients to medical wards, 9% of patients had at least one episode of hypoglycemia [15].

T1D

People with T1D are bound to have hypoglycemia; as they attempt to achieve euglycemia, they will suffer numerous episodes of asymptomatic hypoglycemia. Plasma glucose concentrations may be <50 mg/dL (2.8 mmol/L) 10% of the time. They have an average of two episodes of hypoglycemia per week, thousands of such episodes over a lifetime, and an episode of severe hypoglycemia approximately once a year [7]. Population data indicate that 30–40% of people with T1D experience an average of one to three episodes of severe hypoglycemia each year. Older estimates were that 2–4% of patients with T1D die from hypoglycemia. More recent estimates are that 6–7% or 10% of those with T1D die from hypoglycemia [16].

In the DCCT (Diabetes Control and Complications Trial), severe hypoglycemia occurred in 65% of patients with T1D treated intensively and 35% of patients with T1D on the conventional group over 6.5 years. There were no statistical differences in hospitalizations; however, there were two fatal motor vehicle accidents in the intensive therapy group, which may be attributed to hypoglycemia. The DCCT also confirmed that the presence of detectable endogenous insulin as measured by residual C-peptide secretion is associated with a reduced risk of hypoglycemia [17].

Ninety percent of the surviving cohort of DCCT joined the EDIC (Epidemiology of Diabetes Interventions and Complications), which was an observational follow-up study to examine the long-term effects of the original DCCT therapies. Around 50% of participants in each group reported an episode of severe hypoglycemia during the 20 years of EDIC. The main characteristics, HbA1c (glycated hemoglobin), and hypoglycemia events can be seen in Table 45.3 [18].

There was a group of participants who reported four or more episodes of hypoglycemia. During the DCCT, 54% of the intensive group and 30% of the conventional group experienced more than four episodes of severe hypoglycemia. In the EDIC, 37% of the intensive group and 33% of the conventional group experienced four or more episodes. A subset of participants (14%) experienced nearly one-half of all severe hypoglycemia in the DCCT, and 7% in the EDIC experienced almost one-third of all episodes of severe hypoglycemia. This observation exposes the possibility that there are certain individuals who are more susceptible to severe hypoglycemia [18].

In a retrospective epidemiological survey of an unselected population with T1D, the prevalence of severe hypoglycemia was reported to be 37% over a 1-year recall period, with 130 events occurring per 100 patient-years. In this report, 5% of the participants experienced 54% of all severe hypoglycemia [20].

T2D

Overall, the frequency of hypoglycemia is substantially lower in T2D than in T1D. Event rates for severe hypoglycemia are

Table 45.3 Clinical Characteristics of Patients Enrolled in the DCCT/EDIC Trial (1982-2005)

	Conventional			Intensive treatment		
	DCCT	DCCT/EDIC	EDIC	DCCT	DCCT/EDIC	EDIC
	1 year	6 years	12 years	1 year	6 years	12 years
Characteristics	(*n* = 730)	(*n* = 723)	(*n* = 606)	(*n* = 711)	(*n* = 698)	(*n* = 620)
Age (years)	27 ± 7	33 ± 7	46 ± 7	27 ± 7	34 ± 7	46 ± 7
DM duration (years)	5 ± 4	12 ± 5	24 ± 5	6 ± 4	12 ± 5	25 ± 5
BMI	24 ± 3	25 ± 3	28 ± 5	23 ± 3	27 ± 4	28 ±
HbA1c%	8.9 ± 1.6	9.1 ± 1.5	7.7 ± 1.2	8.9 ± 1.6	7.4 ± 1.1	7.8 ± 1.2
Hypoglycemia coma/seizures[a]	5.4	16.4	9.2	16.3	6.7	13.6
SH[a]	18.7	47.3	39.6	61.2	38.5	48.4

DM diabetes mellitus, *BMI* body mass index (kg/m^2), *HbA1c* hemoglobin A1c, *SH* severe hypoglycemia
Adapted from [18, 19]
[a] Events per 100 patient-years

approximately tenfold lower in T2D even during aggressive insulin therapy. They are even lower in those treated with oral hypoglycemic agents. Most episodes of hypoglycemia in T2D are considered to be mild to moderate [21].

Miller et al. performed a cross-sectional study on T2D African American population. Hypoglycemia had a prevalence of 24.5%, and severe hypoglycemia had a prevalence of 0.5%. The prevalence of hypoglycemia was highest on patients receiving triple therapy, followed by those receiving insulin alone or a single oral agent, and infrequent on those receiving hypoglycemic agents alone or diet therapy alone. In all treatment groups, the prevalence of hypoglycemia tended to increase as HbA1c decreased. The highest prevalence was seen in patients receiving insulin therapy who had HbA1c less than 7% [22].

Over 6 years in the UKPDS (United Kingdom Prospective Diabetes Study), major hypoglycemia was reported in 2.4% of T2D patients treated with metformin, 3.3% of patients treated with sulfonylurea, and 11.2% of those treated with insulin. They found a higher frequency of hypoglycemia in the intensive group compared with the conventional group. With intensive treatment, hypoglycemia occurred most frequently in the insulin-treated patients, and the prevalence of hypoglycemia was lower in the first decade of the study that in later years [8].

Oral and Injectable Agents

Hypoglycemia with oral agents medications occurs most frequently with sulfonylureas and meglitinides. Both classes of medications have increased the absolute risk of hypoglycemia by 4–9% compared to placebo or other agents. Sulfonylureas have an 11% higher risk of hypoglycemia than metformin [23].

Metformin

When used as monotherapy, metformin has minimal risk of hypoglycemia. When compared with placebo, hypoglycemia was reported in less than 5% of patients taking metformin alone. Since metformin enhances insulin sensitivity, when combined with other medications that increase circulating levels of insulin, the risk of hypoglycemia increases [24].

Alpha-Glucosidase Inhibitors

The risk of hypoglycemia is very low; however, should patients experience hypoglycemia, it cannot be treated with sucrose or fruit juice (which is hydrolyzed to glucose and fructose), since the absorption is inhibited by the mechanism of these medications. Hypoglycemic episodes must be treated with simple sugars such as oral glucose (dextrose), which can be in glucose tablets, or grapes [24].

Sulfonylureas

The risk of hypoglycemia is very common with sulfonylureas, even when administered as monotherapy. The rates of hypoglycemia differ with each sulfonylurea based on each agent's pharmacokinetic properties. Glyburide (glibenclamide) has been associated with a higher incidence of hypoglycemia when compared to glipizide. Glyburide should be avoided in patients with creatinine clearance of <50 mL/min.

In randomized clinical trials, sulfonylureas are associated with a significant greater risk of any or severe hypoglycemia when compared to insulin sensitizers or incretin-based therapies. A meta-analysis that included trials with a duration of >24 weeks, enrolling patients with T2D, comparing sulfonylurea with placebo or active drugs different from sulfonylureas, reported that hypoglycemia, including severe hypoglycemia, was frequent in patients treated with sulfonylureas. They also found that the risk of hypoglycemia with sulfonylureas is not different from that of insulin in head-to-head trials. The overall risk of severe hypoglycemia was increased more than threefold with sulfonylureas than with comparators. The cumulative incidence of hypoglycemia with sulfonylureas was 17% and for severe hypoglycemia 1.2% [25].

Amylin

Amylin analogues are associated with a high risk of hypoglycemia when they are combined with insulin therapy. Pramlintide carries a black box warning that when adding pramlintide to insulin, the prandial insulin dose must be reduced by 50% and titrated up to avoid severe hypoglycemia.

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

DPP-4 inhibitors generally do not cause hypoglycemia when used as monotherapy, are weight neutral, and are relatively well tolerated.

Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitors

SGLT2 inhibitors have been shown to have a low risk of hypoglycemia with monotherapy [24].

Insulin

Glargine

Insulin glargine is a long-acting insulin analogue, which is less soluble at physiologic pH (potential of hydrogen) than human insulin. Insulin glargine reduces the risk of nocturnal hypoglycemia in T1D patients compared with insulin NPH (neutral protamine Hagedorn or isophane insulin) when taken either with prandial unmodified human insulin or rapid-acting insulin analogues [20, 26].

Detemir

This is a long-acting basal insulin that has extended duration due to molecular modifications leading to increased albumin binding. Detemir has also been associated with reduced nocturnal hypoglycemia in people with T1D compared with NPH insulin, as reported in numerous studies. In studies comparing twice-daily insulin detemir to NPH insulin, where both groups used a fast-acting insulin analogue prandially, significant reductions in hypoglycemia had been attained with detemir [20, 26].

Degludec

Insulin degludec is an ultra-long-acting insulin analogue, which forms a subcutaneous depot and is slowly released. Studies comparing insulin degludec with glargine have reported a reduced number of nocturnal hypoglycemic episodes in the degludec group.

Insulin degludec was compared with insulin glargine U100 in the SWITCH 1 and SWITCH 2 trials. Both studies used a randomized, double blind, treat-to-target, crossover design. Patients with T1D ($N = 501$; SWITCH 1) or patients with T2D ($N = 721$; SWITCH 2) who had one or more risk factors were enrolled. These patients were randomized to either insulin degludec or insulin glargine U100 for 32 weeks (16-week titration and then 16-week maintenance) and then crossed over to the alternate insulin treatment for an additional 32 weeks (16-week titration and 16 week maintenance). In SWITCH 1, the rate of overall symptomatic hypoglycemia was significantly lower with insulin degludec than insulin glargine U100 (2200.9 vs. 2462.7 episodes/100 patient-years of exposure). In SWITCH 2, the rates of severe hypoglycemia were also statistically significantly lower with insulin degludec than insulin glargine U100 (185.6 vs. 265.4 episodes/100 patient-years) [27–29].

Glargine U300

Another prolonged-acting insulin analogue is insulin glargine U300 [30, 31] (300 IU/mL). By being more concentrated, it forms a compact subcutaneous depot with a smaller surface area to produce a more gradual and prolonged release. Compared to glargine U100, it has shown lower event rates of nocturnal hypoglycemia. Glargine U300 can be injected with a 3 h flexible regimen.

There are pharmacokinetics studies [30] that compare degludec to glargine U300. The clinical studies have not shown a significant difference in the rate of hypoglycemia between the two types of insulin [32].

Fast-Acting Insulin Analogues

Fast-acting insulin analogues were developed in order to better stimulate the physiological postprandial insulin response. Data from subsequent clinical trials comparing lispro with human insulin suggest that the more physiologic pharmacokinetics are associated with a reduced risk of nocturnal hypoglycemia. A multicenter randomized, double blind, crossover study with 90 participants demonstrated a significantly reduced severe hypoglycemia as well as improved glycemic control with insulin aspart compared with human insulin. Fast-acting insulin analogues have shown to reduce nocturnal and late postprandial hypoglycemia [20].

Clinical Manifestations

For people with diabetes, the detection of hypoglycemic symptoms is a critical tool for the recognition and treatment of hypoglycemia. Recognition of hypoglycemia is possible through self-monitoring blood glucose (SMBG), continuous glucose monitoring (CGM), and detection of hypoglycemic symptoms. Numerous biological and psychological modifiers can either facilitate or interfere with the recognition of hypoglycemia. With experience, individuals develop beliefs concerning their symptoms of hypoglycemia. Nevertheless, beliefs have a high incidence of false alarm rates; individuals with poor control may believe that they have hypoglycemia when instead they have hyperglycemia, and individuals with tight control may have hypoglycemia unawareness and not be able to recognize an episode of hypoglycemia. When blood glucose falls too low, then consciousness becomes impaired, making it difficult to accurately interpret the meaning of any symptom. Some people may deny symptoms of hypoglycemia because symptoms represent failure in their self-management [33].

Symptoms of hypoglycemia are divided into two categories (Table 45.4):

- Autonomic (neurogenic) symptoms are the result of perception of physiological changes caused by the autonomic nervous system release triggered by hypoglycemia.

Table 45.4 Symptoms of hypoglycemia

Autonomic	Neuroglycopenic
Adrenal	Slowed thinking
• Trembling	Abnormal mentation
• Shakiness	Irritability
• Palpitations	Confusion
• Nervousness	Difficulty speaking
• Anxiety	Ataxia
• Pupil dilation	Paresthesias
• Pallor	Headaches
Cholinergic	Stupor
• Clamminess	Seizures
• Sweating	Coma
• Hunger	Death (if untreated)
• Tingling	

Adapted from [34]

- Neuroglycopenic symptoms occur as a result of brain neuronal glucose deprivation. The patient usually recognizes these symptoms first.

Physical signs that result from activation of the sympathoadrenal system include pallor and diaphoresis, which are often prominent, and increased heart rate and systolic blood pressure, which are often subtler. Hypothermia is often present. Transient focal neurological deficits (diplopia, hemiparesis) occur occasionally [7].

Symptoms of hypoglycemia vary greatly among patients and depend on the individual's personal experience and sensitivity. In mild hypoglycemia, symptoms result from an ANS response and usually consist of tremors, palpitations, sweating, blurred vision, mood variations, and excessive hunger. Major cognitive deficits usually do not accompany mild reactions, so patients are generally able to self-treat. These mild symptoms usually respond to an oral ingestion of 10–15 g of carbohydrates and resolve within 10–15 min. Moderate hypoglycemia includes neuroglycopenic as well as autonomic symptoms, which usually consist of headache, mood changes, irritability, decreased attentiveness, and drowsiness. Behavioral changes such as irritability, agitation, quietness, stubbornness, and tantrums may be the prominent symptoms for the preschool child and may result from a combination of neuroglycopenic and autonomic response [5]. People often need assistance in treating themselves, and these reactions produce longer-lasting and more severe symptoms usually requiring a second dose of carbohydrates. Severe hypoglycemic symptoms are characterized by unresponsiveness, combativeness, unconsciousness, or seizures and typically require assistance from another individual. Patients who experience seizures with severe hypoglycemia are at risk for recurrence [35, 36].

Diagnosis and Detection

People may recognize hypoglycemia based on their symptoms and experience, although as discussed earlier, individuals may not be aware of an episode of hypoglycemia or may misinterpret their symptoms. It has been reported that patients who are being typically aware of their hypoglycemia, on average, recognize 50% of their hypoglycemic episodes [36]. Therefore, documentation of a low plasma glucose concentration is very helpful. A hypoglycemic episode is most convincingly documented by the Whipple's triad: symptoms compatible with hypoglycemia, a low plasma or blood glucose concentration, and restoration of those symptoms after the glucose concentration is raised to normal [8].

There are two technologies available to measure glucose in an outpatient setting: capillary measurement with point-of-care glucose meters or self-monitoring blood glucose (SMBG) and interstitial measurement with CGM, both retrospective and real time [1].

Additional Facts

- Plasma glucose samples are up to 15% higher than mixed venous whole blood glucose samples.
- Mixed venous blood glucose values can be considerably lower than arterial or capillary levels.
- Glucose meters can be imprecise, especially at low blood glucose levels [14].

Causes

The need to identify underlying causes is an important aspect of hypoglycemia evaluation and management. Looking back over the events of several hours preceding the reactions can often identify the factors precipitating an event of hypoglycemia (Table 45.5).

Table 45.5 Conventional causes of hypoglycemia

Insulin (or secretagogues or insulin sensitizers) doses are excessive, ill-timed, or of wrong type
Exogenous glucose delivery is decreased
• Missed meal
• Low carbohydrate meal
• Overnight fast
• Vomiting
Endogenous glucose production is decreased
• Alcohol ingestion
Glucose utilization is increased
• Exercise
• Sepsis, trauma, burns
Sensitivity to insulin is increased
• Late after exercise
• Weight loss
• Improved fitness
Insulin clearance is decreased
• Renal failure
• Liver failure
• Hypothyroidism

Adapted from [8]

Risk Factors and Determinants

Many factors can put T1D and T2D patients at increased risk of experiencing hypoglycemia (Table 45.6). Severe hypoglycemia is mostly associated with the use of glucose-lowering drugs, especially insulin or insulin secretagogues.

In a large retrospective cohort study involving people with T2D, severe hypoglycemia was recorded in 12 cases per 10,000 patient-years. They observed approximately six times higher incidence rate in patients using insulin during follow-up than in non-insulin users. Patients with cardiovascular disease and renal failure had approximately 1.5 times higher incidence rate of severe hypoglycemia. In this study, the current use of insulin or sulfonylureas, age ≥75, renal failure, and cognitive impairment/dementia were associated with a substantially increased risk of developing severe hypoglycemia in the overall population [34].

The Fremantle Diabetes Study was a longitudinal observational cohort study aimed at defining the determinants of severe hypoglycemia complicating T2D. Insulin treatment or its duration, renal impairment, peripheral neuropathy, and higher education proved to be independent predictors of first and multiple episodes of hypoglycemia. The frequency of hypoglycemia was also associated with a lower fasting serum glucose but paradoxically higher HbA1c. A prominent predictor of the first episode of hypoglycemia in this cohort was duration of insulin treatment, with each year increasing the risk by 33%. They also found that a previous history of hospitalization for severe hypoglycemia was a strong independent predictor of the first episode of hypoglycemia [37].

Table 45.6 Risk factors for hypoglycemia

Insulin deficiency
Negative C peptide
Long-standing diabetes
History of severe hypoglycemia
Hypoglycemia unawareness
Extremes of age (young and elderly)
Cognitive impairment/dementia
Systemic illness
• Renal failure
• Liver failure
• Congestive heart failure
Ethanol use
Autonomic neuropathy
Glucose variability
Aggressive glycemic therapy
Peripheral neuropathy
Lower glycemic goals
Medications
• Fixed insulin regimens
• Sulfonylureas
• Salicylates
• Beta blockers
• Coumarin
• Fibrates
Nutritional factors
• Ethanol consumption
• Gastroparesis
• Fasting or missed meals
• Malnutrition
• Low-carb diets
Nocturnal hypoglycemia
Erratic schedules
Exercise (especially irregular)
Hormonal factors
• Adrenal insufficiency
• Hypothyroidism
• Hypopituitarism
• Pregnancy/breastfeeding
• Allopurinol
• Nonsteroidal anti-inflammatory drugs (NSAIDs)

Physical Activity and Exercise

Physical activity may increase glucose transport and utilization by skeletal muscles, acutely and chronically. Hypoglycemia can occur during 1–2 h after exercise, or up to 17 h after exercise. Aerobic exercise results in an increase in both insulin- and non-insulin-mediated glucose uptake [38, 39].

The blood glucose response to exercise is affected by many factors including duration, intensity and type of exercise, the time of day when exercise is performed, plasma glucose, insulin levels, and the availability of supplemental and stored carbohydrates [5].

During moderate intensity exercise in nondiabetic individuals, endogenous insulin secretion is reduced by 40–60% [40]. The increased fuel demands on the working muscle necessitate compensatory metabolic processes in the liver and kidney. Changes in hepatic glycogenolysis and gluconeogenesis have been found to be closely coupled to the increase in glucose uptake produced by the working muscle because of the actions of the pancreatic hormones. The exercise-induced increase in glucagon secretion and the concomitant decrease in insulin secretion interact to stimulate hepatic glycogenolysis, whereas the increase in hepatic gluconeogenesis is determined primarily by gluca-

gon's action to increase hepatic gluconeogenic precursor fractional extraction and the efficiency of intrahepatic conversion to glucose. Epinephrine and norepinephrine become important in increasing glucose production during prolonged or heavy exercise. Catecholamines can produce this effect by directly stimulating both hepatic and renal glucose production, by increasing the availability of gluconeogenic precursors (lactate, alanine, or glycerol), and by increasing lipolysis. Catecholamine-induced metabolic effects at the muscle and adipose tissue are rapid, increasing gluconeogenic precursor uptake at the liver within minutes [7].

Recent studies have demonstrated that there is a vicious cycle of counterregulatory failure between exercise and hypoglycemia. Thus, two episodes of prolonged, moderate-intensity exercise can reduce ANS and neuroendocrine responses by 50% during subsequent similar hypoglycemia. Similarly, two episodes of antecedent hypoglycemia can reduce counterregulatory responses during subsequent exercise by 40–50%. Therefore, individuals who have had a previous episode of hypoglycemia are at greater risk of hypoglycemia during exercise [40].

In a randomized crossover study involving subjects with T1D, participants were randomly assigned to morning exercise versus afternoon exercise. They found that morning exercise confers a lower risk of late-onset hypoglycemia than afternoon exercise and improves metabolic control on the subsequent day [39].

Alcohol

Ethanol induces hypoglycemia by inhibiting gluconeogenesis; as little as 50 g of alcohol might be sufficient. Alcohol excess, especially in the fasting state, is a major risk factor for severe hypoglycemia. Ethanol and its metabolism influence several pathways vital for the manufacture and production of glucose by the liver [41].

The gluconeogenesis pathway is disrupted with ethanol ingestion by

- Reduced nicotinamide adenine dinucleotide NADH/NAD ratio—as a result of the oxidation of alcohol to acetaldehyde and acetate, thus reducing the ability of the liver and kidney to oxidize lactate and glutamate to pyruvate and alpha-ketoglutarate.
- Inhibiting the release of alanine from the muscle (a vital precursor of gluconeogenesis)
- Inhibition of lactate, glycerol, and alanine uptake by the liver

Alcohol potentiates the hypoglycemic effect of insulin and sulfonylureas, and because of the inhibition of gluconeogenesis, glucagon and catecholamines are ineffective in raising glucose levels [7].

Moderate consumption of alcohol in the evening may predispose patients to hypoglycemia on the subsequent morning with reduced nocturnal growth hormone secretion [5].

Medications

Beta-Blockers

Propranolol and other nonselective beta-blockers decrease the ability of the liver and kidney to increase their release of glucose, enhance peripheral insulin sensitivity, and may mask the symptoms of hypoglycemia. The risk of hypoglycemia becomes even higher in the presence of renal dysfunction. The hypoglycemic effect of beta-blockers seems to be directly tied to the diminished adrenergic response to hypoglycemia and to the diminished concentration of circulating free fatty acids. Therefore, propranolol should be used with caution or, if possible, avoided in patients with renal failure. Recent studies indicate that beta-1 selective blockers do not present an increased risk for severe hypoglycemia and therefore should not be considered as being contraindicated in diabetic patients.

- Salicylates—Salicylates can act by binding hepatic glucose production and increasing insulin secretion.
- Sulfonamides—Have a chemical structure similar to sulfonylureas and have been known to have blood glucose-lowering properties.
- Angiotensin-converting enzyme inhibitors can increase insulin sensitivity and can decrease the degradation of bradykinin, which has certain insulin mimetic actions.
- Pentamidine is cytotoxic to pancreatic beta cells, and hypoglycemia occurs with the release of insulin from degenerating cells [7].

Renal Failure

Renal insufficiency is a very common predisposing condition for hypoglycemia. In fact, it is probably the second most common potentiating factor of hypoglycemia after insulin therapy. Nearly 50% of hospitalized patients who were recognized to have hypoglycemia had chronic renal failure. The mortality rate in patients with chronic renal failure may be related to the degree of hypoglycemia and to the number of risk factors for hypoglycemia. In renal failure, hypoglycemia may result from the use of insulin, antidiabetic agents, certain drugs, or a combination of the above [42].

Hypoglycemia resulting from an oral hypoglycemic agent in patients with renal failure is more likely to occur when other factors such as hepatic dysfunction, hypoalbuminemia, alcoholism, or an associated endocrine deficiency are pres-

ent. It is usually manifested by neuroglycopenic symptoms rather than neurogenic symptoms, and patients may display atypical symptoms. Hypoglycemia is usually of long duration, particularly when a sulfonylurea is the causal agent.

Congestive Heart Failure

The occurrence of congestive heart failure in patients with renal failure may also precipitate hypoglycemia. The pathogenesis of hypoglycemia in heart failure is varied and involves liver dysfunction resulting from congestion, poor nutrition, cachexia, and poor blood supply to muscles and liver. Insufficient production or delivery of substrates for adequate gluconeogenesis in the liver, severe depletion of glycogen stores, possibly caused by poor dietary intake, and gastrointestinal malabsorption caused by congestive heart failure are major potentiating factors of hypoglycemia. The coexistence of renal failure and congestive heart failure may place the patient at even higher risk for hypoglycemia.

Sepsis, Trauma, and Burns

Initially, the response to the stress of infection is an increase in glucose turnover, with glucose production often exceeding glucose utilization and resulting in mild hyperglycemia. This response involves increases in both glycogenolysis and gluconeogenesis and is largely mediated by glucagon. As the infection worsens, increased release of endotoxin and its derivatives, complement activation, endoperoxide activation, and release of endogenous inflammatory mediators (tumor necrosis factor-alpha, interleukins, and other monokines) compromise cardiovascular integrity and cause central venous pooling, inadequate tissue perfusion, and microvascular protein transudation. At this stage, a decrease in splanchnic and renal blood flow occurs. Despite concomitantly reduced peripheral tissue perfusion, glucose utilization is increased. Decreased tissue oxygenation causes increased anaerobic glycolysis, which perpetuates the increased glucose utilization [7].

The inability of glucose production to keep pace with increased tissue demands results in hypoglycemia. Hepatic glycogen stores are rapidly exhausted; consequently, glucose production becomes solely dependent on gluconeogenesis. However, gluconeogenesis fails because of a reduction in ANS and neuroendocrine effects.

Glucose Variability

It has been shown that glucose variability is associated with increased risk of hypoglycemia. In an observational study involving people with T2D, they found that hypoglycemia was positively associated with glucose variability and negatively associated with mean glucose concentration. The risk of hypoglycemia was completely or virtually eliminated when the glucose variability was <30 mg/dL (<1.7 mmol/L). Therefore, lowering glycemia without reducing glucose variability should be avoided as it places the individual at greater risk of hypoglycemia [43].

Nocturnal Hypoglycemia

It has been estimated that about one-half of hypoglycemia episodes occur during sleep. Hypoglycemia, including severe hypoglycemia, occurs most commonly during the night in people with T1D.

The counterregulatory responses to hypoglycemia are attenuated during sleep, leading to HAAF syndrome; also, insulin sensitivity is enhanced during the middle of the night. Furthermore, sleep often precludes recognition of warning symptoms of developing hypoglycemia and thus appropriate response [22, 38].

Pregnancy

Normal blood glucose levels in pregnant women are 20% lower than in nonpregnant women. A great number of metabolic changes occur during pregnancy to make women more vulnerable to hypoglycemia. Pregnancy itself is associated with suppression of glucose counterregulatory responses [7].

Maternal hypoglycemia during pregnancy is a risk factor for newborns small for gestational age, which in turn is associated with increased long-term risks such as development of diabetes, coronary artery disease, and hypertension [14].

For women with T1D, severe hypoglycemia occurs three to five times more frequently in the first trimester and at a lower rate in the third trimester when compared with the incidence in the year preceding pregnancy. Risk factors for severe hypoglycemia in pregnancy include history of severe hypoglycemia, hypoglycemia unawareness, long duration of diabetes, low HbA1c in early pregnancy, glucose variability, excessive use of insulin. When pregnant and nonpregnant women are compared with CGM, mild hypoglycemia (defined by the authors as <60 mg/dL or 3.3 mmol/L) is more common in all pregnant women. For women with preexisting diabetes, insulin requirements rise throughout the pregnancy and then drop precipitously at the time of delivery of the placenta, requiring an abrupt reduction in insulin dosing to avoid post-delivery hypoglycemia.

Breastfeeding may also be a risk factor for hypoglycemia in women with insulin-treated diabetes [1].

Elderly

Hypoglycemia is a common problem in old people with diabetes. Aging modifies the cognitive, symptomatic, and counterregulatory hormonal responses to hypoglycemia. The effect of aging on increased risk of unawareness or severe episodes of hypoglycemia has also been recognized. Older individuals may have multiple risk factors for hypoglycemia such as renal impairment, chronic heart disease, malnutrition, and polypharmacy.

In older individuals, episodes of hypoglycemia are more likely to be followed by changes in the blood-brain circulation, which may further increase the risk of neurological damages in this population [12].

Severe hypoglycemia has a considerable impact on the well-being, productivity, and quality of life of old people with diabetes.

Children and Adolescents

It is now well recognized that although many physiologic responses are similar across the age groups, there can be significant developmental and age-related differences in children and adolescents. The DCCT reported a higher rate of severe hypoglycemia in adolescents as compared to adults, 86 vs. 57 events requiring assistance per 100 patient-years, despite adolescents having poorer control with HbA1c levels approximately 1% higher. There are a number of physiologic and behavioral mechanisms that contribute to this difference. First, there are behavioral factors such as variable adherence that have been clearly associated with poor glycemic control in adolescents. Second, during puberty, adolescents with or without T1D are more insulin resistant than adults. During hypoglycemia, adolescents with or without diabetes release catecholamines, cortisol, and growth hormone at higher glucose levels than adults. However, intensively treated young adults with T1D counterregulate and experience hypoglycemia symptoms at a lower glucose level, suggesting a greater susceptibility to hypoglycemia in the young [5].

Young children with T1D are noted as particularly vulnerable to hypoglycemia because of their reduced ability to recognize hypoglycemic symptoms and effectively communicate their needs [2].

Children with early-onset diabetes, particularly those diagnosed before age 6, and severe episodes of hypoglycemia have an increased range of cognitive dysfunction and brain abnormalities. Repeated hypoglycemic seizures in young children may also cause structural brain damage [12].

Hypoglycemia Impact

There are several major concerns about the risks of hypoglycemia as it may cause severe morbidity and even death. One vulnerable organ is the brain, which is markedly dependent on glucose as a fuel for normal functioning. Brain dysfunction or damage may occur, and it may cause permanent damage. Among the severe manifestations of hypoglycemia is sudden death, which may not be directly linked to the effects of hypoglycemia. Cardiovascular consequences of hypoglycemia include alteration of ventricular repolarization. Hypoglycemia creates a prothrombotic state and may predispose to ischemic injury. Additional studies have established associations between hypoglycemia and the development of cardiac arrest and cerebral ischemia and cardiac arrhythmias [38, 44].

Hypoglycemia and Cardiovascular Disease

Patients with diabetes have an increased risk of cardiovascular disease, as it is the most common cause of diabetes-related deaths. Intensive glucose control increases the risk of hypoglycemia and severe hypoglycemia. Several epidemiological studies have linked hypoglycemia to increased cardiovascular risk, as it will be discussed further [42].

Acute hypoglycemia causes pronounced physiological responses as a consequence of autonomic activation, principally of the sympathoadrenal system, and results in end-organ stimulation and a profuse release of epinephrine. This profound autonomic response provokes hemodynamic changes. The magnitude of the counterregulation is directly proportional to the depth of hypoglycemia. Blood flow is increased to the myocardium, the splanchnic circulation, and the brain. There are also an increase in heart rate and peripheral systolic blood pressure, a fall in central blood pressure (reducing peripheral resistance), and an increase in myocardial contractility, stroke volume, and cardiac output. The workload of the heart is therefore markedly increased [45].

Increased plasma viscosity occurs during hypoglycemia due to an increase in erythrocyte concentration. Also, coagulation is promoted by platelet activation and increase in factor VIII and von Willebrand factor. Endothelial function may be compromised due to an increase in C-reactive protein. Soluble vascular cell adhesion molecule 1, soluble intracellular adhesion molecule 1, and soluble E-selectin are increased from baseline under hypoglycemic conditions. Soluble P-selectin, plasminogen activator inhibitor 1, tissue plasminogen activator, von Willebrand factor, and platelet-monocyte aggregation were measured by Joy and colleagues and found to be significantly increased during hypoglycemia and returned to baseline during normoglycemia [44, 45].

Hypoglycemia in ACCORD, ADVANCE, and VADT

These three studies randomized almost 24,000 patients with long-standing T2D to standard or intensive glycemic control for up to 5 years, ensuring HbA1c levels <7%. All three trials were carried out in participants with either known cardiovascular disease or multiple risk factors. Strict glycemic control did not incur a significant cardiovascular benefit, and none of the trials demonstrated a positive effect on cardiovascular events of mortality. In fact, the ACCORD study was interrupted prematurely because of an excess mortality in the intensive group. In all three trials,

Table 45.7 Clinical Characteristics, ACCORD/ADVANCE Clinical Trials

		ACCORD		ADVANCE		VADT	
Participants		10,251		11,140		1791	
Age (years)		62		66		60	
Men/women (%)		61/39		58/42		97/33	
BMI (kg/m^2)		32.2 ± 5.5		28 ± 5		6.9 ± 8.5	
Diabetes duration (years)		10		8		11.5	
History of CVD%		32		28		31	
Mean HbA1c%		8.1		7.2		9.4	
HbA1c%	HbA1c%	6.4	7.5	6.5	7.3	6.9	8.5
Intensive	Standard						
Hypoglycemia	Hypoglycemia	16.2	5.1	2.7	1.5	21.2	1.5
Intensive %	Standard %						
On insulin at baseline %		35		1.5		52	
Insulin	Insulin	77	55	40	24	89	74
Intensive %	Standard %						
Mean duration of follow-up		3.5 (terminated early)		5		5.6	
CVD		35%		34%		40%	
Primary CVD end point		↓ 10% ($p = 0.16$)		↓ 6% ($p = 0.37$)		↓ 13% ($p = 0.12$)	
Mortality (overall)		↑ 22% ($p = 0.012$)		↓ 7% (p = NS)		↑ 6.5% ($p = 0.12$)	
CV mortality		↑ 35% ($p = 0.02$)		↓ 12% (p = NS)		↑ 25% (p = NS)	

Based on [45, 46]

hypoglycemia was significantly higher in the intensive glucose-lowering arms compared with the standard arm. Symptomatic severe hypoglycemia was associated with an increased risk of death within each study arm. In the VADT study, a recent severe hypoglycemic event was an important predictor of cardiovascular death and all-cause mortality (Table 45.7) [45, 46].

It is possible that severe hypoglycemia could increase the risk of cardiovascular death in patients with underlying cardiovascular risk.

Cardiac Arrhythmias

Hypoglycemia has been known to cause electrocardiographic changes with lengthening of the corrected QT (QTc) interval and cardiac repolarization, exerting a pro-arrhythmogenic effect. Other electrocardiographic abnormalities observed during hypoglycemia include a decrease in PR interval and depressed T waves [44]. Abnormal cardiac repolarization appears to be related to the sympathoadrenal stimulation and release of catecholamines and to the hypokalemia that results from the insulin effect. In an observational study of patients with T1D, the effect of nocturnal and daytime hypoglycemia was assessed on EKG (electrocardiogram) with CGM. They found that hypoglycemia was common and had different distinct patterns in the EKG. Bradycardia was commonly seen while patients had nocturnal hypoglycemia, while with daytime hypoglycemia, they had more atrial ectopy. Prolonged QTc, T-peak to T-end interval duration, and decreased T wave symmetry were detected during nocturnal and daytime hypoglycemia [47]. Cardiovascular autonomic neuropathy or impairment is associated with increased mortality.

Cognitive Function and Dementia

Repeated severe hypoglycemia over time may impair cognitive function or damage the brain. Patients with T1D and a history of severe hypoglycemia have a slight but significant decline in intelligence scores in comparison with matched controls. Magnetic resonance imaging (MRI) in small studies of patients with T1D with no history of severe hypoglycemia when compared with patients with T1D with a history of five or more episodes of severe hypoglycemia has found cortical atrophy in nearly half of those who had a history of severe hypoglycemia. Severe hypoglycemia has been known to induce focal neurological deficits and transient ischemic attacks, which are reversible with the correction of blood glucose. Recent studies suggest that recurrent and severe hypoglycemia may predispose to long-term cognitive dysfunction and dementia [42, 44].

A number of studies have observed a relationship between dementing illness and diabetes. Both hyperglycemia and hypoglycemia potentially are implicated in the increased risk of dementing illness most commonly observed in elderly patients [12].

Dead-in-Bed Syndrome and Sudden Death

The "dead-in-bed" syndrome is an uncommon fatal event thought to be responsible for 6% of deaths of patients with

T1D who are younger than 40 years old. In 1991, Tattarsall and Gill described 22 cases of unexplained death that they labeled as dead-in-bed syndrome. Possible contributors to dead-in-bed syndrome are hypoglycemic brain damage, autonomic neuropathy, cardiac events such as arrhythmias, and electrolyte abnormalities. Nocturnal hypoglycemia is of substantial concern because patients may be "unaware" and susceptible to serious sequelae. Tanenberg reported a 23-year-old patient with T1D who died in his undisturbed bed from hypoglycemia. Postmortem download of the data in the CGM demonstrated glucose below 30 mg/dL around the time of his death and a vitreous humor glucose of 25 mg/dL [48].

Prolonged, profound hypoglycemia can cause brain death. The mechanism is thought to be sustained increased plasma glutamate release and receptor activation when plasma glucose concentrations are <18 mg/dL (1.0 mmol/L), the electroencephalogram is isoelectric, and brain glucose and glycogen levels are immeasurably low.

Quality of Life

Hypoglycemia can have a significant impact on patients' health-related quality of life, treatment satisfaction, and cost of diabetic management. The well-being of patients may be affected both directly from the effects of hypoglycemia and indirectly from fear of recurrence. Nocturnal hypoglycemia may impact one's sense of well-being on the following day because of its impact on sleep quality and quantity. Patients with recurrent hypoglycemia have been found to have chronic mood disorders including depression and anxiety. Interpersonal relationships may suffer as a result of hypoglycemia in patients with diabetes. Hypoglycemia also impairs one's ability to drive a car [1, 12].

In the UKPDS, patients reporting more frequent hypoglycemic episodes also reported increased tension, mood disturbances (anger, fatigue), and less work satisfaction. In the RECAP-DM study, participants with hypoglycemia reported significantly lower scores on scales for effectiveness, convenience, and global satisfaction than patients who did not have hypoglycemia, with concomitant barriers to treatment adherence. In this study, patients reporting symptoms of hypoglycemia were in general more markedly affected by their illness, had significantly lower self-rated general health, and had more worries about hypoglycemia than participants without hypoglycemia [49].

Fear of Hypoglycemia

When people experience hypoglycemia and its unpleasant symptoms, this has been shown to result in fear of future hypoglycemia. This concept may compromise overall glycemic control and impair quality of life. Recent, frequent, or severe hypoglycemia episodes tend to exacerbate this fear, while useful strategies to reduce the frequency of hypoglycemia, such as insulin pump adjustments or CGM, may alleviate such fear. There is clearly concern about the adverse consequences of hypoglycemia. These concerns primarily include damage to the brain and increased cardiovascular risk. Fear of hypoglycemia sometimes leads to deliberate undertreatment with insulin therapy [38].

A large study with 764 participants concluded that the frequency of severe hypoglycemia is the most important factor in the development of fear of hypoglycemia.

A retrospective study of 335 participants with either T1D or T2D found that hypoglycemia and fear of future hypoglycemia had an impact upon T1D and T2D patients. Self-treatment was the predominant means of coping with mild or moderate and severe hypoglycemia. Following mild or moderate event, neither T1D nor T2D patients utilized healthcare resources and did little more than mention the episode to their physician. Severe hypoglycemia was shown to have a considerable impact upon patient lifestyle. A major alteration to daily activities was noted with respect to fear of driving [50].

Fear of hyperglycemia is a psychological construct characterized by excessive worry about high blood glucose in combination with acceptance (and non-avoidance) of hypoglycemia—as a necessary evil to evade the development of long-term complications. It may lead to inappropriate blood glucose-lowering behaviors, including deliberate overtreatment or overzealous use of insulin, reluctance to attend to the early symptoms of hypoglycemia, and inappropriate pursuit of low blood glucose despite recurrent hypoglycemia.

Critical Illness and Hospitalization

Persons with diabetes are three times more likely to be hospitalized than those without diabetes, and approximately 25% of hospitalized patients (including people without a history of diabetes) have hyperglycemia. Inpatient hyperglycemia has been associated with prolonged hospital length of stay and with numerous adverse outcomes including mortality. Several studies have shown that aggressive lowering of glycemia in the ICU is not beneficial, markedly increases the risk of severe hypoglycemia, and may be associated with increase mortality [1].

A cohort of 33,675 hospitalized patients with and without diabetes, followed for almost 3 years, found that hypoglycemia, insulin related or non-insulin related, was associated with increased short- and long-term mortality. In this study, patients with moderate hypoglycemia during hospitalization had a more than twofold increase in mortality

compared with patients without hypoglycemia. Severe hypoglycemia was associated with a threefold increase in mortality [14].

Treatment of Hypoglycemia

Treatment is aimed at restoring euglycemia, preventing recurrences, and, if possible, alleviating the underlying cause. Providers should continue to counsel patients to treat hypoglycemia with fast-acting carbohydrates at a hypoglycemia alert value of 70 mg/dL or less. This should be reviewed at each patient visit. Hypoglycemia requires ingestion of glucose or carbohydrate-containing foods. The acute glycemic response correlates better with the glucose content of food than with the carbohydrate content of food. Pure glucose is the preferred treatment, but any form of carbohydrate that contains glucose will raise blood glucose. Added fat may retard and then prolong the acute glycemic response. In T2D, ingested protein may increase insulin response without increasing plasma glucose. Therefore, carbohydrate sources high in protein should not be used to treat or prevent hypoglycemia. Ongoing insulin activity or insulin secretagogues may lead to recurrent hypoglycemia unless more food is ingested after recovery. Once glucose returns to normal, the individual should be counseled to eat a meal or snack to prevent recurrent hypoglycemia [2].

Mild Hypoglycemia

When the patient can self-treat, mild hypoglycemia is managed with the oral administration of 15–20 g of oral carbohydrate. This should be repeated every 15–20 min until glucose is >70 mg/dL (3.9 mmol/L). Treatment and follow-up testing should be repeated if hypoglycemia persists. Several sources of short-acting carbohydrate exist (Table 45.8). Employing premeasured glucose products instead of juice or food is recommended, because patients tend to consume more than 15 g of juice or food, and additional calories from fat or protein may cause weight gain. Commercially available glucose tablets have the added benefit of being premeasured to help prevent overtreatment [36].

The glycemic response to oral glucose is transient, typically <2 h. Therefore, ingestion of a snack or meal shortly after the plasma glucose or SMBG is raised is generally advisable [8].

Table 45.8 Sources of carbohydrates

	Portion	Carbohydrates
Glucose products (preferred)		
Glucose tablets	1 tablet	4 g
Glucose gel	1 gel	15 g
Insta-glucose gel	1 tube	24 g
Food/beverage (if the aforementioned are not available)		
Juice	½ cup (200 mL)	15–20 g
Soft drink (regular)	½ cup (200 m)	15–20 g
Syrup or honey	1 tbsp	6 g
Sugar	2 tbsp in water	8 g

Based on [34, 38]

Key Points

- Rule of thumb—15 g of carbohydrate will raise blood glucose at around 50 mg/dL.
- Rule of 15 (15 × 15): 15 g of carbohydrate every 15 min until the SMBG level is >70 mg/dL (3.9 mmol/L) [40].

Moderate Hypoglycemia

Individuals with moderate reactions will often respond to oral carbohydrates but may require more than one treatment and take longer to fully recover. These patients may be alert but will frequently be uncooperative or belligerent.

Severe Hypoglycemia

Severe hypoglycemia requiring assistance of a second or third party should be assessed in the hospital setting. Patients with impaired consciousness or an inability to swallow may aspirate and should not be treated with oral carbohydrate. These patients require either parenteral glucagon or intravenous glucose. If these are not available, glucose gels, applied between the patient's cheek and gum, may be of some help until professional care arrives.

Glucagon

The use of glucagon is indicated for the treatment of hypoglycemia in people unable or unwilling to consume carbohydrates. Those in close contact with, or having custodial care of, people with hypoglycemia-prone diabetes (family members, roommates, school personnel, childcare providers, correctional institutional staff, or coworkers) should be instructed on the use of glucagon, including where the glucagon product is kept and when and how to administer it. An individual does not need to be a healthcare professional to safely administer glucagon [2].

Currently available glucagon preparations are injectable glucagon emergency kits, recently approved nasal glucagon, and liquid glucagon rescue pen. When delivered correctly,

glucagon is efficacious as a rescue therapy for severe hypoglycemia [51].

Glucagon Emergency Kits

Recombinant crystalline glucagon is available as a lyophilized powder that is mixed with an aqueous diluent to a concentration of 1 mg/dL. Because aqueous glucagon is unstable, it must be used immediately; the currently available glucagon emergency kits contain powdered glucagon that must be reconstituted using a multiple-step process before the drug can be administered parenterally [5]. The dose of glucagon needed to treat moderate or severe hypoglycemia for children <5 years old is 0.25–0.50 mg; for older children (aged 5–10 years), 0.50–1 mg, and for those >10 years old, 1 mg. Glucagon should be given intramuscularly or subcutaneously in the deltoid or anterior thigh region. Glucagon can cause nausea or vomiting, and patients should be placed on their side to reduce the risk of aspiration. The effects of glucagon are delayed by approximately 10 min from the time of injection and are only inducible in those with available glycogen stores [14, 36].

Nasal Glucagon

It is a ready-to-use drug/device combination to treat severe hypoglycemia in people with diabetes aged >4 years. A 3 mg dose of nasal glucagon powder, which does not require reconstitution, is administered in the patient's nostril. Nasal glucagon is passively absorbed through the anterior nasal mucosa without the need for inhalation, making it suitable for a comatose person with profound neuroglycopenia.

The effectiveness and ease of use of nasal glucagon (3 mg) in moderate or severe hypoglycemia events were evaluated in two real-world studies involving adults, children, and adolescents with T1D. Nasal glucagon was effective in resolving 96% of hypoglycemia events in adults within 30 min. All severe events were resolved within 15 min. The time to nasal glucagon administration was <30 s for most hypoglycemic events. Most common symptoms related to nasal glucagon administration were nasal irritation and headache. Nausea and vomiting were reported in 13%.

Nasal glucagon can be delivered by a caregiver of a person experiencing a severe hypoglycemic event using a compact, portable, single-use device with no reconstitution required.

Administration of nasal glucagon is faster and has much higher success rate for the delivery of the full dose with fewer errors than injectable glucagon [5, 51].

Liquid Glucagon Rescue Pen

A novel, ready-to-use, body temperature-stable rescue pen containing liquid glucagon was recently approved for the treatment of severe hypoglycemia in people with diabetes aged 2 years and older. The glucagon rescue pen is available in two premeasured doses: 0.5 mg for pediatric use and 1.0 mg for use in adolescents and adults. Administration of glucagon with the rescue pen is a two-step process, with no need for reconstitution [51].

Emerging Rescue Therapies for Severe Hypoglycemia

BioChaperone Glucagon

A stable, ready-to-inject, aqueous formulation of human glucagon, BioChaperone glucagon (BCG) is currently being developed to treat severe hypoglycemia.

Dasiglucagon

Dasiglucagon is a novel stable peptide analogue of human glucagon in an aqueous solution at neutral pH, with improved physical and chemical stability compared with currently available glucagon formulations [51]. This formulation is being tested in the bi-hormonal closed loop system insulin pump.

Remember

- Family members or responders should avoid sublingual placement of carbohydrate in an unconscious or impaired individual because this can increase the risk of aspiration.
- Place the patient on their side to reduce the risk of aspiration.
- Those in close contact with people with hypoglycemia-prone diabetes should be instructed on the use of glucagon.

Intravenous Glucose

If medical staff and equipment are available, intravenous glucose should be given as a primary treatment in preference to glucagon. Comatose patients should receive intravenous glucose. The usual dose is 25 g of 50% dextrose in water (D50) over 1–3 min. D50 comes in 50 mL; therefore, administration of 25 mL is equivalent to 12.5 g of carbohydrate. Sustained intravenous infusion of dextrose 5% (D5) or dextrose 10% (D10) at 100 cm^3/h should follow, aimed at keeping the blood glucose level at approximately 80–100 mg/dL (4.4–5.6 mmol/L) to avoid hyperglycemia, causing further

stimulation of insulin release and setting in motion a vicious cycle. Blood glucose levels should be monitored initially every 15–30 min for at least 2 h or longer depending on the etiology [7, 36].

Additional Facts

- D50 is an irritant, and delivery through a large gauge port and vein, followed by a saline flush, is preferable.
- Alternatively, D10 and D5 are less irritating and can be administered via a peripheral vein in a proportionally higher volume [14].

Treatment of Hypoglycemia After Exercise

Several approaches are used to minimize hypoglycemia risk with exercise. In those injecting insulins, meal insulin doses taken a few hours before exercising often are reduced by one-half for moderate activity (such as 30-min walk) to one-quarter or less for vigorous activity, such as running or swimming. Both the intensity and the duration of activity influence the need for adjustments. The meal immediately after exercising also usually will require some reduction in dose [36].

With insulin pumps, an added benefit is the ability to reduce basal rates using temporary basal infusions. During and for a period of time after vigorous exercise, reductions in 40–90% are not uncommon [36].

Snacks taken before exercise may provide protection against hypoglycemia episodes during exercise or for a short time afterward. Some people prefer not to use fast-acting carbohydrate but instead use a mixed snack with protein, fat, and carbohydrate. It is important to make the distinction between eating to prevent hypoglycemia and eating to treat hypoglycemia. Mixed snacks are less rapidly effective in raising low blood glucose and should not be preferred to pure dextrose or other rapidly effective treatment when hypoglycemia is occurring [36].

Strategies to Reduce or Prevent Hypoglycemia

Prevention

The prevention of hypoglycemia is preferable to its treatment. Improving glycemic control while minimizing hypoglycemic episodes represents a challenge but can be accomplished safely. Physicians can use this three-step strategy to minimize hypoglycemia [8]:

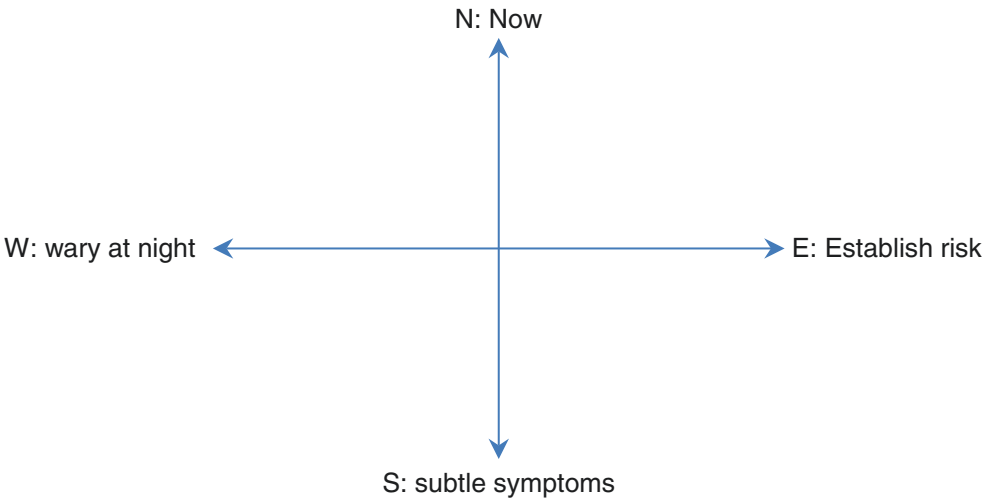
1. Addressing the issue of hypoglycemia in each patient encounter. This should be addressed in each patient visit.

   If patients report a history of hypoglycemia, details regarding the time of episodes need to be identified and the treatment regimen adjusted accordingly [40]. It is important to determine what the patient's symptoms were. When did they occur in relation to the patient's last meal, and what was the patient doing when the episode occurred? Was it an isolated event, or had it occurred before? How frequently do they occur? Is there any pattern to the occurrences? How long have these events been occurring? Did weight gain or weight loss occur during this period? Is the patient taking any other medication? Did the patient lose consciousness? If so, were premonitory sings present? Was the hypoglycemia documented? Did the patient recover spontaneously? What did the patient do to prevent recurrences or relieve symptoms?
2. Applying the principles of aggressive therapy. The principles of aggressive glycemic therapy include the following:
   (a) Patient education and empowerment
   (b) Frequent SMBG
   (c) Flexible insulin and other drug regimens
   (d) Individualized glycemic goals
   (e) Professional guidance and support

   Education regarding all aspects of diabetes care is important in the prevention and treatment of hypoglycemia. Carbohydrate counting, insulin and oral medication dosing, concomitant medications, alcohol intake, exercise, and even driving should be included in the discussion. Education will help alleviate fear of hypoglycemia that may impede ideal glycemic control.

   The Blood Glucose Awareness Training (BGAT) program is a behavioral intervention designed to improve avoidance, prediction, recognition, and treatment of hypoglycemia and hyperglycemia. Classically, BGAT consists of eight weekly group sessions during which participants are trained in behavioral techniques (self-monitoring and direct feedback) and symptoms awareness and educated about food, exercise, and insulin. Studies have reported a significantly improved detection of low blood glucose and reduced frequency of hypoglycemia and hyperglycemia, particularly in people with impaired awareness of hypoglycemia from baseline to 6 months. Benefits are maintained at 12-month follow-up with significantly fewer severe hypoglycemic events. In 2008, BGAT was adapted for Internet delivery, with data demonstrating that education can be made easily accessible to large numbers [20].

Fig. 45.4 HypoCOMPaSS



An education program has been developed in Germany, which focuses specifically on hypoglycemia. HyPOS consists of five weekly 90-min sessions, during which participants learn about hypoglycemia as a "vicious cycle" and are trained in symptom awareness (using diaries and SMBG). A randomized controlled trial comparing HyPOS to standard T1D education in 164 participants with impaired awareness or severe hypoglycemia found significant improvements in awareness as measured by the validated Clarke questionnaire and a modified version of the Gold score. No difference was detected in either severe hypoglycemic rate or overall glycemic control. At long-term (31 months) follow-up, incidence of severe hypoglycemia was lower in the HyPOS group with 12.5% compared with 26.5% in the controlled group [20].

The Dose Adjustment for Normal Eating (DAFNE) T1D education program that was derived from a training program developed in Düsseldorf provides a holistic approach to improving glycemic control. There is growing evidence suggesting that it reduces severe hypoglycemia and improves hypoglycemia awareness [20].

The four points of the HypoCOMPaSS (Fig. 45.4) are as follows: never delay hypoglycemia treatment, recognize personalized times of increased risk, detect subtle symptoms, and detect symptoms through regular self-monitoring, particularly for nocturnal hypoglycemia. In a multicenter randomized controlled clinical trial, the HypoCOMPaSS program was used in 110 adults with negative C-peptide T1D and impaired hypoglycemia awareness. They found that hypoglycemia awareness can be improved and recurrent severe hypoglycemia prevented in adults with long-standing T1D and impaired awareness through strategies delivered in clinical practice, targeted at rigorous avoidance of biochemical hypoglycemia without relaxation of overall control. Biochemical hypoglycemia was rapidly reduced in all groups within the first 4 weeks, driven by the insulin dose adjustment algorithm and sustained throughout the 24-week trial [52].

3. Considering both the conventional risk factors and those indicative of compromised glucose counterregulation [8].

Hypoglycemic episodes that are not readily explained by conventional factors, for example, skipped or irregular meals, unplanned exercise, alcohol ingestion, etc., may be due to excessive doses of medications used to treat diabetes. A thorough review of blood glucose patterns may suggest vulnerable periods of the day that mandate adjustments to current medications.

A history of severe iatrogenic hypoglycemia is a clinical red flag. Unless it was the result of an obviously remediable factor, such as a missed meal after insulin administration or vigorous exercise without appropriate regimen adjustment, a substantive change in the regimen must be made. If it is not, the risk of recurrent severe hypoglycemia is unacceptably high.

In patients injecting insulin, the following strategies can help minimize hypoglycemia. With basal-bolus insulin regimen, morning fasting hypoglycemia implicates the long- or intermediate-acting insulin. Daytime hypoglycemia may be caused by the rapid, fast, or longer-acting insulins. Nocturnal hypoglycemia may also be caused by rapid and longer-acting insulins. Substitution of preprandial regular insulin with fast-acting insulin (lispro, aspart, glulisine) reduces the frequency of daytime hypoglycemia. Similarly, substitution of a long-acting insulin analogue (glargine, detemir, degludec) for intermediate-acting insulins such as NPH or premix 70/30 also reduces the frequency of nocturnal or daytime hypoglycemia [8].

With a CSII regimen using a fast-acting insulin such as lispro, nocturnal and morning fasting hypoglycemia implicate the basal insulin infusion rate, whereas daytime

hypoglycemia may implicate the preprandial insulin bolus doses, the basal insulin infusion rate, or both.

Insulin secretagogues can also produce hypoglycemia related to absolute or relative insulin excess. However, sulfonylureas may pose the greatest risk of hypoglycemia in patients with altered renal or hepatic function and in older individuals. Substitution with other classes of oral agents or even GLP-1 receptor agonists (GLP-1 RA) should be considered in the event of hypoglycemia.

In patients with clinical hypoglycemia unawareness, a 2- to 3-week period of scrupulous avoidance of hypoglycemia is advisable and can be assessed by return of awareness of hypoglycemia.

Strategies to Reduce Hypoglycemia

Since the first injection of insulin in 1922, interest has increased in replacing insulin in the most physiologic manner for patients with diabetes. In the 1980s, the introduction of recombinant human insulin reduced the formation of antibodies and provided more predictable pharmacokinetic profiles. The next decade produced analogue insulins that initially were designed to provide a faster onset and shorter duration of action. These insulins (lispro, aspart, glulisine) were designed to reproduce more closely the typical physiologic prandial spikes of insulin observed following meals.

The second wave produced long-acting basal types of insulin (glargine U100, detemir) and more recently ultra-long-acting analogues (degludec, glargine U300) designed to mimic background constitutive insulin release. Studies in T1D have demonstrated that hypoglycemia (particularly nocturnal) can be reduced with fast-acting analogues rather than regular insulins. Similarly, long-acting analogues have been demonstrated to reduce hypoglycemia by 20–33% in patients with T2D when compared with NPH-based regimens. Thus, current recommendations are to use analogue-based insulin replacement whenever possible [7].

Technology in the Reduction and Prevention of Hypoglycemia

The rapid technological advances in the management of diabetes with CGM systems or integrated CGM and insulin pump use have empowered individuals with T1D to further address and reduce hypoglycemia.

Continuous Glucose Monitoring

Advances in technology have allowed the development of real-time continuous glucose monitoring (CGM) devices that can be programmed to alarm in response to failing glucose or when hypoglycemia or hyperglycemia occurs or is predicted. CGM devices provide a broad spectrum of information on real-time glucose trends. Currently available CGM devices measure interstitial glucose concentrations subcutaneously at 5- to 15-min intervals.

CGM can be divided into three categories: blinded/retrospective CGM, real-time CGM, and intermittently scanned/viewed CGM, also known as flash glucose monitoring [53].

Randomized controlled trials (RCTs) evaluating the benefit of CGM mainly focused on HbA1c as the primary outcome. Apart from the SWITCH study showing a significant effect of adding CGM to insulin pump therapy on time spent in hypoglycemia, most studies failed to demonstrate a significant or relevant reduction in mild hypoglycemia. Notably, RCTs primarily aimed at hypoglycemia prevention did demonstrate a significant reduction in mild hypoglycemia in terms of reducing the time spent in hypoglycemia by approximately 40% and reducing the number of mild hypoglycemic events per day [53].

In patients with T1D and impaired hypoglycemia awareness, data from a recent RCT and from an observational study suggested reduced severe hypoglycemia using CGM compared with SMBG.

Real-time CGM can reduce the frequency of severe hypoglycemia in people with impaired awareness of hypoglycemia and in those with long-standing T1D.

Continuous Subcutaneous Insulin Infusion (CSII)

Commonly known as insulin pump therapy, CSII has been recommended by several professional organizations as a therapeutic option for T1D complicated by problematic or severe hypoglycemia [20].

Insulin pump development began in the 1970s and over the last 20 years has become a major method of insulin replacement. Studies in children and pregnant women have demonstrated reduction in hypoglycemia when compared with MDI regimens [7].

A review and meta-analysis that only included studies of more than 6-month duration, comparing the frequency of severe hypoglycemia and the associated HbA1c during MDI and CSII, revealed a significant reduction in severe hypoglycemia in people with T1D who used CSII compared with the non-analogue-based MDI. However, most of the trials used NPH insulin as the basal insulin [54].

In multiple trials comparing CSII with multiple daily injections (MDI), there has been a modest improvement in HbA1c; however, the majority of the systematic reviews have failed to confirm a significant reduction in severe hypoglycemia. A Cochrane review found no relevant benefit of

CSII over multiple daily injections (MDI) for reducing non-severe hypoglycemic events, but data indicated a possible benefit of CSII over MDI in terms of reducing severe hypoglycemia [55]. As these meta-analyses are based on clinical trial data obtained prior to 2008, the pumps utilized are at least 10 years older than the current technology available; thus, they lack some more advanced features now available on newer pumps.

In the HypoCOMPaSS trial, the authors concluded that the restoration of hypoglycemia unawareness and the prevention of hypoglycemia could be achieved with either self-monitoring blood glucose (SMBG) and MDI or CSII and RT-CGM (real-time continuous glucose monitoring) when management is truly optimized using fast-acting and basal insulin analogues with appropriate therapeutic targets and regular SMBG including interval nighttime testing [52].

Sensor-Augmented Pumps (SAP)

SAP therapy, defined as a combination of insulin pump and CGM, represents the first step on the path toward an artificial pancreas. The first RCT to insulin pump therapy in those with T1D showed similar reductions in HbA1c after 6 months, but this was associated with significant increased hypoglycemia exposure in the insulin pump with the SMBG group.

The Sensor-Augmented Pump Therapy for A1c Reduction (STAR) 3 study randomized participants to either SAP or maintained them on MDI therapy with conventional SMBG checks for a 1-year study period and reported a greater reduction in HbA1c was associated with an increased frequency of sensor use. Those using SAP were more likely to attain the HbA1c targets and have decreased hypoglycemic exposure and decreased glycemic variability.

Sensor-Augmented Pumps with Low Glucose Suspension (Suspend on Low)

This insulin pump model is connected to a CGM that automatically suspends basal insulin delivery for a maximum of 2 h if the individual does not respond to a hypoglycemia alarm. This has been shown to reduce the duration of hypoglycemia in those with very frequent hypoglycemia at baseline, especially at night. This function also reduces moderate and severe episodes of hypoglycemia in patients with hypoglycemia unawareness. The reduction in hypoglycemia was not associated with deterioration of glucose control or ketosis [5].

The Automation to Simulate Pancreatic Insulin Response (ASPIRE) in-clinic study demonstrated that the mean duration of hypoglycemia was shorter on SAP-suspend on low and the nadir glucose was higher.

The ASPIRE in-home study reported a 37.5% reduction in the primary end point for nocturnal hypoglycemia in the SAP with low suspend vs. SAP alone. Despite this reduction in hypoglycemia, there was no deterioration in glycemic control [51].

An RCT of 247 participants showed that the use of a sensor-augmented insulin pump therapy with the threshold-suspend feature over a 3-month period reduced nocturnal hypoglycemia, without increasing HbA1c levels [56].

Sensor-Augmented Pump Therapy with Predictive Low Glucose Management (Suspend Before Low)

The Predictive Low Glucose Management system suspends basal insulin infusion with the prediction of hypoglycemia. Basal insulin infusion is suspended when sensor glucose is at or within 70 mg/dL (3.9 mmol/L) above the patient-set low limit and is predicted to be 20 mg/dL (1.1 mmol/L) above this low limit in 30 min. In the absence of patient interference, following pump suspension, the insulin infusion resumes after a maximum suspend period of 2 h or earlier if the auto-resumption parameters are met. The PLGM reduced hypoglycemia under in-clinic conditions and in short-term and long-term home studies. There was no deterioration of glycemic control with the use of the system in a 6-month randomized controlled home trial [5].

In 45 participants between the ages of 15 and 45 years, the system reduced hypoglycemia exposure by 81% and time spent <60 mg/dL (<3.3 mmol/) by 70%, while not leading into a difference in blood glucose levels in the morning [53].

Closed Loop Systems

Automated insulin delivery consists of three components: an insulin pump, a continuous glucose sensor, and an algorithm that determines insulin delivery. These systems not only suspend insulin delivery but also can increase insulin delivery based on sensor glucose values. Closed loop systems have been under development for several years with numerous algorithms and tested in clinical research centers, hotels, camps, supervised outpatient settings, and free-living conditions. Despite variable clinical and technical characteristics, artificial pancreas systems uniformly improve glucose control with a 50% relative risk reduction in hypoglycemia in outpatient settings compared to conventional pump therapy. Closed loop systems appear to hold great promise for the future as a tool to help prevent hypoglycemia in T1D [20, 53].

Fig. 45.5 Glycosylated hemoglobin compared with severe hypo rate in patient. (Adapted from [17, 36, 56])

One interesting development has been the evaluation of dual-hormone delivery systems with an additional pump delivery the counterregulatory hormone dasiglucagon, potentially increasing the effect in rescuing failing blood glucose.

The development of newer technologies and devices has made it possible to achieve glycemic control while minimizing the risk of hypoglycemia, first with the CGM and then with SAP (Fig. 45.5).

Beta Cell Replacement

The transplantation of isolated islets or a whole pancreas is a potential therapy for the treatment of T1D, particularly when complicated by recurrent episodes of hypoglycemia. Patients undergoing whole pancreas transplantation require a major surgery and will be on life-long immunosuppressive therapy with a mortality rate of 3–5%. This is why it is largely performed together with kidney transplantation (simultaneous pancreas-kidney or SPK), as they will need immunosuppressive therapy [20, 57].

Both approaches can restore insulin secretion, but the transplantation of islets isolated from more than one donor pancreas is usually necessary to achieve insulin independence. The durability of insulin independence is superior following whole pancreas transplantation, especially when it is SPK.

The magnitude of the beta-cell secretory capacity responses following whole pancreas transplantation appears normal and may be sustained for more than a decade despite ongoing immunosuppression drug exposure. In the absence of immunologic graft loss, the beta-cell secretory capacity can remain stable for years during longitudinal follow-up, while first-phase insulin response to glucose may decrease coincident with lessening of glucocorticoid doses and improvement in insulin sensitivity.

In T1D recipients of intrahepatic islet transplants, there is recovery of the physiologic islet cell hormonal responses to insulin-induced hypoglycemia whereby endogenous insulin secretion is appropriately suppressed and glucagon secretion is partially restored. Rickels and colleagues have demonstrated normalization of the glycemic thresholds for counterregulatory epinephrine, autonomic symptoms, and growth hormone responses in islet transplant recipients with T1D [57].

The CIT-07 Trial (Clinical Islet Transplantation Consortium Protocol 07) was a phase 3 clinical trial of transplantation of islet products in subjects with TID, impaired awareness of hypoglycemia, and intractable severe hypoglycemia. This trial showed that 87.5% of the subjects achieved freedom of severe hypoglycemia along with glycemic control (HbA1c <7%) at 1 year post-initial islet transplantation. The subjects reported consistent, statistically significant, and clinically meaningful improvements in condition-specific health-related quality of life as well as self-assessment of overall health [58].

Pancreas transplantation has been performed in patients with T1D for >25 years. In general, hypoglycemic rates improve dramatically in the first year after transplantation. Most studies also demonstrate that counterregulatory defenses are improved after pancreatic transplantation. Most notably, glucagon response to hypoglycemia increases, accompanied at an early stage by some improvement in epinephrine and symptomatic responses [7].

Concluding Remarks

- Patients with T1D and long-standing T2D have an altered counterregulatory response to hypoglycemia, making them more susceptible.
- Hypoglycemia is a major limiting factor in the management of diabetes; nonetheless, it is possible to improve glycemic control by acknowledging the problem, considering the risk factors, applying the principles of intensive therapy, and individualizing glycemic goals.
- It is possible to achieve optimal glycemic control while minimizing hypoglycemia by structured patient education concerning self-monitoring and appropriate lifestyle and physiologic and flexible insulin regimen.
- As time passes, safer and more physiologic insulin analogues are being manufactured, and novel technologies are being developed, which will facilitate achieving normoglycemia.

Multiple-Choice Questions

1. A 28-year-old T1D patient is experiencing palpitations, anxiety, shakiness, and hunger 2 h after running 10k. He checks his capillary blood glucose and it is 48 mg/dL (2.7 mmol/L). How would you classify this hypoglycemia?
   (a) **Symptomatic hypoglycemia**
   (b) Severe hypoglycemia
   (c) Moderate hypoglycemia
   (d) Hypoglycemia unawareness
   (e) Hypoglycemia-associated autonomic failure
2. An 18-year-old healthy college student is experiencing headaches, palpitations, anxiety, and hunger after a 2-h figure-skating practice; she forgot to eat breakfast before her practice. Her coach performs a capillary blood glucose with a value of 54 mg/dL (3 mmol/L). Which of the following is correct regarding the normal counterregulatory response?
   (a) Glucagon stores are depleted; therefore, cortisol and growth hormone are the principal hormonal response.
   (b) As blood glucose levels fall, there is an increased release of insulin, glucagon, and epinephrine within minutes to increase glycogenolysis and gluconeogenesis.
   (c) There is a decreased brain glucose uptake; therefore, epinephrine and cortisol will rise within minutes to increase glycogenolysis and gluconeogenesis.
   (d) **The first response is a decreased insulin level, followed by an increase in glucagon and epinephrine.**
3. A 35-year-old patient with long-standing T1D had a morning capillary blood glucose of 36 mg/dL (2 mmol/L). He denies any symptoms of hypoglycemia, although he has been having difficulty sleeping and nightmares. Which of the following statements is correct regarding his counterregulatory response to hypoglycemia?
   (a) As blood glucose levels decrease, his insulin levels will not decrease; therefore, glucagon and epinephrine become the critical response and will increase within minutes.
   (b) Cortisol and growth hormone become the principal response, since there is deficient release of glucagon and epinephrine.
   (c) **The patient is experiencing hypoglycemia unawareness, with blunted glucagon and epinephrine responses.**
   (d) Insulin levels do not decrease, and glucagon response becomes impaired; therefore, epinephrine becomes a critical response and will rise within minutes.
4. A 75-year-old patient with long-standing T2D is experiencing frequent episodes of hypoglycemia. He has background retinopathy, symmetrical neuropathy, and nephropathy with an estimated GFR of 50 mL/min. The patient states that he sometimes misses his meals. His last HbA1c was 7.5%. He is on glyburide, metformin, and bedtime insulin NPH. What changes in management will decrease his episodes of hypoglycemia?
   (a) Change insulin NPH to a more physiologic long-acting insulin analogue.
   (b) His HbA1c is at goal; ensure the patient does not skip meals and advise him to take snacks between meals.
   (c) Advise the patient to decrease the dose of his NPH by half.
   (d) **Discontinue glyburide, but continue the same dose of insulin NPH.**

5. A 35-year-old female patient with T1D had an episode of hypoglycemia on Sunday morning. Her basal insulin dose was recently increased since her fasting capillary blood glucose was not at goal. She has been experiencing abdominal cramps and fatigue as she started her menstrual period on Friday. On Saturday, she had a light dinner with two cups of wine and administered fast-acting insulin according to her carbohydrate counting. What is the most likely cause of her hypoglycemia?
   (a) The increase in her basal insulin dose.
   (b) Hormonal imbalance due to her menstrual period.
   (c) The fast-acting insulin dose was excessive.
   (d) **Alcohol intake.**
6. A 59-year-old patient with long-standing T1D with microvascular complications (diabetic proliferative retinopathy, diabetic nephropathy (estimated GFR of 45 mL/min), distal symmetric neuropathy, autoimmune hypothyroidism, dyslipidemia, and ischemic heart disease) is experiencing frequent episodes of hypoglycemia. The patient is on a flexible insulin regimen with a basal insulin analogue and a fast-acting insulin analogue, aspirin, beta-1 selective blocker, angiotensin-converting enzyme inhibitor (ACEI), and levothyroxine. His last HbA1c was 7.8%, TSH 3.2 mUI/L, and Cr 1.8 mg/dL. Which of the following confers the greatest risk for hypoglycemia?
   (a) Age
   (b) Background retinopathy
   (c) **Diabetic nephropathy**
   (d) Ischemic heart disease
   (e) HbA1c level
   (f) Current medications: insulin, salicylate, beta-selective blocker, ACEI
   (g) Hypothyroidism
7. A 65-year-old patient with long-standing T2D with a history of background retinopathy, autonomic neuropathy, diabetic nephropathy, and ischemic heart disease is experiencing frequent episodes of hypoglycemia. He had an acute myocardial infarction with subsequent coronary artery bypass grafting (CABG) a few months ago. He is on metformin, NPH insulin, statin, beta blocker, aspirin, and angiotensin receptor blocker. His HbA1c is 7%. Which of the following is the most appropriate statement?
   (a) He needs tight glycemic control to decrease the progression of microvascular complications.
   (b) His HbA1c is at goal; therefore, changing insulin NPH to insulin analogue will decrease the risk of subsequent hypoglycemia while ensuring optimal glycemic control.
   (c) **He has high cardiovascular risk; therefore, his HbA1c goal should be higher; consider decreasing his insulin NPH.**
   (d) He has high cardiovascular risk; therefore adding an SGLT2 inhibitor will decrease his cardiovascular risk.
8. What are the clinical implications of hypoglycemia on a patient with long-standing T2D and ischemic heart disease, diabetic nephropathy, diabetic retinopathy, and peripheral neuropathy?
   (a) Hypoglycemia may accelerate the progression of diabetic retinopathy to proliferative retinopathy.
   (b) Hypoglycemia is associated with worsening of glomerular filtration rate and proteinuria.
   (c) **Hypoglycemia can increase his cardiovascular risk by triggering arrhythmias or thromboembolic events.**
   (d) Repeated hypoglycemia may worsen his peripheral neuropathy.
9. A 68-year-old patient with T2D is brought to the emergency department with altered mental status. He is awake but very confused and combative. He has a history of alcohol abuse. He is currently on basal insulin analogue, sulfonylureas, and metformin. He has a blood glucose level of 35 mg/dL. Which of the following is the most appropriate treatment for this patient?
   (a) 15–20 g of carbohydrate every 15 min until his blood glucose is more than 70 mg/dL and then provide a meal.
   (b) 1 mg of intramuscular glucagon, placing the patient on his side to ensure that he does not aspirate.
   (c) Administer 25 g of 50% dextrose over 1–3 min, and discharge the patient when his blood glucose is more than 70 mg/dL.
   (d) **Administer a bolus of dextrose 50%, and then continue with IV glucose infusion 5–10% for 2–3 days, checking blood glucose every hour.**
10. A 15-year-old patient with T1D is experiencing frequent noon and nocturnal hypoglycemia. The patient frequently misses meals, has erratic schedules, and gets confused with her insulin regimen. Which of the following strategies will most likely decrease her risk of subsequent hypoglycemia.
    (a) Write down a prescription with a detailed insulin regimen and advise the patient to eat at a regular basis and avoid missing meals.
    (b) Organize a meeting with her parents addressing the importance of regular meals and explain in detail and writing her insulin regimen.
    (c) **Explain to the patient the importance of SMBG, explain in detail and in writing her insulin regimen, explain the importance of regular meals, and schedule an appointment with a diabetes educator.**
    (d) Change the insulin regimen to a fixed dose so the patient does not get confused.

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Inpatient Management of Diabetes and Hyperglycemia

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William B. Horton

Introduction

Individuals with diabetes mellitus (DM) are more likely to be hospitalized and have longer durations of hospital stay than those without DM [1]. Approximately one in four patients admitted to the hospital has a known diagnosis of DM [2, 3], and about 30% of patients with DM require two or more hospitalizations in any given year [3]. A 2007 study estimated that 22% of all hospital inpatient days were incurred by people with DM and costs associated with hospitalization for DM patients accounted for half of all healthcare expenditures for the disease [4]. Given the increasing incidence and prevalence of DM in the Unites States since that time [5], it is likely that these figures have only increased.

Recent studies show that one-third of all hospitalized patients will experience significant hyperglycemia [6], and patients without preexisting DM can even experience stress-related hyperglycemia while hospitalized [7]. Uncontrolled hyperglycemia in inpatients with or without a previous diagnosis of DM is associated with numerous adverse outcomes, including postoperative complications and mortality [2, 8–14]. This association is observed for both admission blood glucose (BG) and mean BG level throughout hospitalization [15]. Inpatient hyperglycemia has been specifically linked to increased duration of hospital stay, increased incidence of infection, increased mortality, and greater disability after hospital discharge in various studies [2, 16–20]. Observational and randomized controlled studies indicate that improved glycemic control results in lower rates of hospital complications in general medicine and surgery patients [15] and decreased length of hospital stay [7]. Moreover, inpatient glycemic control is cost-effective [1]. In the Portland Diabetic Project, initiation of continuous intravenous (IV) insulin therapy to achieve predetermined target BG values in patients with DM undergoing open-heart surgical procedures reduced the incidence of deep sternal wound infections by 66%, resulting in a total net savings of $4638 per patient [21]. In another study, intensive glycemic control in 1600 patients treated in a medical intensive care unit (ICU) was associated with a total cost savings of $1580 per patient [22]. With mounting evidence demonstrating the value of reducing both hyper- and hypoglycemia, optimizing inpatient glycemic control should be a priority for all healthcare providers.

Recognition and Diagnosis of Hyperglycemia and Diabetes on Admission

Inpatient hyperglycemia is defined as any BG value >140 mg/dL (7.8 mmol/L) [1, 15] and can occur not only in patients with known DM but also in those with previously undiagnosed DM and others who experience "stress hyperglycemia" during an acute illness or procedure [1, 15, 23, 24]. Various studies have identified hyperglycemia in 32–38% of patients in community hospitals [2, 25], 41% of critically ill patients with acute coronary syndromes [13], 44% of patients with heart failure [13], and 80% of post-cardiac surgery patients [26, 27]. In these studies, approximately one-third of non-critically ill patients and 80% of critically ill patients had no history of DM prior to admission [2, 13, 28–31].

Current guidelines recommend the initiation of BG monitoring for those with DM and those without a known history of DM who are receiving therapies associated with hyperglycemia [32]. Further sources suggest that an initial BG measurement on admission is appropriate for all hospitalized patients, regardless of the presence of preexisting DM or exposure to known inducers of hyperglycemia [15]. Guidelines also recommend that all inpatients with known DM or hyperglycemia be assessed with a laboratory measure of hemoglobin A1c (if this has not been performed in the preceding 3 months), both for diagnosis of DM and identification of patients at risk for DM [15, 32]. Hemoglobin A1c (HbA1c) values ≥6.5% suggest, in previously undiagnosed

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patients, that DM preceded hospitalization [33]. Measurement of HbA1c during periods of hospitalization also provides the opportunity to identify patients with known DM who might benefit from intensification of their glycemic control regimen [15]. In patients with newly diagnosed hyperglycemia, HbA1c may help differentiate patients with previously undiagnosed DM from those with stress-induced hyperglycemia [34, 35].

Therapeutic Agents and Regimens for Inpatient Glycemic Control

For many reasons, inpatient hyperglycemia is best managed with insulin therapy. Patients with type 1 diabetes mellitus (T1DM) have an absolute insulin requirement and necessitate treatment with basal plus prandial insulin regimens to avoid severe hyperglycemia and ketoacidosis [15]. Patients with type 2 diabetes mellitus (T2DM) are often treated with a variety of therapies in the outpatient setting, including diet, lifestyle modifications, oral agents, non-insulin injectable medications, insulin, and/or any combination of these options [15]. However, the use of oral and other non-insulin therapies presents many challenges in the inpatient setting, as there are frequent contraindications to their use in hospitalized patients (e.g., sepsis, IV contrast dyes, pancreatic disorders, renal dysfunction, etc.) [1]. The majority of hospitalized patients will not be proper candidates for regimens other than insulin therapy, and each class of oral antidiabetic therapies possesses characteristics that may limit their desirability for inpatient use [6]. Despite these concerns, it should be noted that in certain circumstances, it may be appropriate to continue home regimens including oral glucose-lowering medications [32]. Clinical judgment should be used by the healthcare provider to evaluate patient criteria for the continued use of these agents in the hospital, including patients who are clinically stable and eating regular meals along with having no specific contraindications to the use of certain oral antidiabetic drugs [15]. Several recent randomized trials have demonstrated the potential effectiveness of glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors in specific groups of hospitalized patients [32, 36–39]. Their inpatient use, however, remains limited by the fact that GLP-1 receptor agonists can cause nausea and should be withheld in acutely ill inpatients [6] and that a Food and Drug Administration (FDA) bulletin advised discontinuation of the DPP-4 inhibitors saxagliptin and alogliptin in patients who develop heart failure [40]. Safety and effectiveness data for sodium-glucose cotransporter-2 (SGLT2) inhibitors are currently lacking; thus, these agents are not recommended for routine inpatient use [32].

Insulin works reliably and can be quickly titrated based on changes in diet or glucose levels, making it ideal therapy in the inpatient setting [41]. For insulin-naive patients with BG levels >140 mg/dL (7.8 mmol/L) who are eating regular meals, insulin therapy can safely be initiated at a total daily dose of 0.2–0.5 units/kg body weight [42–45]. The lower starting dose is advised for leaner patients and those with renal dysfunction, while the higher starting dose is recommended for obese patients and those receiving glucocorticoids [6]. Fifty percent of the calculated total daily dose should be given as a basal component, and the remaining 50% should be split into thirds and given preprandially as the meal component [42, 43]. Patients who are NPO may receive basal insulin alone plus correctional doses with a rapid-acting analog every 4 h or regular insulin every 6 h [15, 17, 44]. Table 46.1 provides examples of basal plus prandial insulin regimens along with correctional dose protocols for inpatient glycemic control in non-critically ill inpatients.

Patients (either T1DM or T2DM) already receiving treatment with insulin prior to admission should continue treatment with a scheduled subcutaneous (SC) insulin regimen during admission [15]. These patients should have their insulin regimen modified according to clinical status both upon admission and throughout hospitalization as a way to reduce the risk for both hypo- and hyperglycemia [15]. The home total basal and prandial insulin dose should be reduced on admission for patients with poor nutritional intake, impaired kidney function, or admission BG levels <100 mg/dL (5.6 mmol/L) [15].

Finally, it should be noted that using sliding scale insulin (SSI) as the sole method for glycemic control of hospitalized patients is an ineffective therapy that should be avoided [15]. Scheduled basal plus prandial (BPP) insulin regimens mimic normal pancreas hormonal physiology and are designed to prevent hyperglycemia, whereas SSI alone only attempts to lower hyperglycemia after it has occurred [6]. SSI as sole management for inpatient hyperglycemia has routinely been shown to provide suboptimal glycemic control [46–49], and its regular use has been described as providing "action without benefit" [50]. Despite mounting evidence showing the inferiority of SSI alone, it remains ingrained in the practice of some healthcare facilities [51]. Clinician fear of hypoglycemia, clinical inertia, and resistance to institutional change have all been suggested as factors contributing to the continued use of SSI monotherapy in the inpatient setting [52]. A study comparing scheduled BPP insulin to SSI alone showed a significantly higher percentage of patients achieving goal BG levels in the BPP group than in the SSI group (66% vs. 38%) without an increase in hypoglycemia [45]. In another study [48], the risk for hyperglycemia (defined as BG >200 mg/dL or 11.1 mmol/L) was three times greater in patients managed with aggressive SSI regimens. For inpatients requiring insulin therapy to manage hyperglycemia,

Table 46.1 Basal plus prandial and correctional dose insulin regimens for glycemic control of the non-critically ill patient

A. Basal insulin orders			
• Calculate TDD as follows:			
– 0.2–0.3 units/kg body weight per day in patients: aged ≥70 years and/or GFR <60 mL/min			
– 0.4 units/kg body weight per day for patients not meeting the criteria above who have BG concentrations of 140–200 mg/dL (7.8–11.1 mmol/L)			
– 0.5 units/kg body weight per day for patients not meeting the criteria above when BG concentration is 201–400 mg/dL (11.2–22.2 mmol/L)			
• Distribute total calculated dose as approximately 50% basal insulin and 50% prandial insulin			
• Give basal insulin once (e.g., glargine) or twice (e.g., NPH) daily, at same time each day			
• Give rapid-acting (i.e., prandial) insulin in three equally divided doses before each meal. Hold prandial insulin if patient is unable to eat			
• Adjust insulin doses based on bedside POCT BG measurements			
B. Supplemental (correction) rapid-acting insulin analog or regular insulin			
Supplemental insulin orders			
• If a patient is able and expected to eat all or most of his/her meals, give rapid-acting insulin before each meal and at bedtime following the "usual" column (*Section C below*)			
• If a patient is unable to eat, give regular insulin every 6 h or rapid-acting insulin every 4–6 h following the "sensitive" column (*Section C below*)			
Supplemental insulin adjustment			
• If fasting and premeal BG are persistently >140 mg/dL (7.8 mmol/L) in the absence of hypoglycemia, increase scale of insulin from the insulin-sensitive to the usual or from the usual to the insulin-resistant column (*Section C below*)			
• If a patient develops hypoglycemia (BG <70 mg/dL or 3.8 mmol/L), decrease regular or rapid-acting insulin from the insulin-resistant to the usual column or from the usual to the insulin-sensitive column (*Section C below*)			
C. Supplemental insulin scale			
BG (mg/dL)	*Insulin sensitive*	*Usual*	*Insulin resistant*
>141–180	2	4	6
181–220	4	6	8
221–260	6	8	10
261–300	8	10	12
301–350	10	12	14
351–400	12	14	16
>400	14	16	18

TDD total daily dose, *GFR* glomerular filtration rate, *BG* blood glucose, *POCT* point-of-care testing
Adapted with permission from Reference [15]
[a] The numbers in each column of *Section C* indicate the number of units of regular or rapid-acting insulin analogs per dose. "Supplemental" dose is to be added to the scheduled insulin dose. Give half of supplemental insulin dose at bedtime. If a patient is able and expected to eat all or most of his/her meals, supplemental insulin will be administered before each meal following the "usual" column dose. Start at the insulin-sensitive column in patients who are not eating, elderly patients, and those with impaired renal function. Start at the insulin-resistant column in patients receiving corticosteroids and those treated with more than 80 units/day prior to admission. To convert mg/dL to mmol/L, divide by 18

BPP insulin regimens are superior to SSI alone and should be the preferred method utilized for glycemic control.

Glycemic Control of the Non-critically Ill Patient

Management strategies and glycemic target values vary by inpatient population and location; thus, an appropriate understanding of the protocols, procedures, and system environments needed to optimize inpatient glycemic control for various patient groups is of vital importance for all healthcare facilities and providers. Non-critically ill patients are hospitalized for management of a wide variety of issues and illnesses, though diabetes and/or hyperglycemia are often not the primary reason for admission. Nevertheless, the benefit of appropriate glycemic control should not be minimized in this scenario.

Glycemic Monitoring

Bedside capillary point-of-care testing (POCT) is the preferred method for guiding ongoing glycemic management of the non-critically ill patient [15]. Recommendations include POCT before meals and at bedtime in patients who are eating regular meals [1, 15]. Matching the timing of POCT with nutritional intake and medication administration is an important component of proper inpatient glycemic control. Premeal POCT should be obtained as close to the time of meal tray delivery as possible and no greater than 1 h before meals [53, 54]. POCT should be performed every 4–6 h in patients who are NPO or receiving continuous enteral (EN) or parenteral (PN) nutrition [1, 15]. More frequent POCT is indicated after a medication change that could affect glycemic control (e.g., glucocorticoid use or discontinuation of EN or PN) [32, 55, 56], or in patients who experience frequent episodes of hypoglycemia [17, 29].

Healthcare providers should be aware of the fact that the accuracy of most POCT meters is far from optimal [57]. Consistent BG sampling sites and methods of measurement should be used because results can vary greatly when alternating between fingerstick and alternative sites, or between samples run in the laboratory and a POCT device [15, 57]. There are also potential inaccuracies of POCT testing including intrinsic issues with technology and variability between different lots of test strips, varying tissue perfusion states and hemoglobin concentrations, and other interfering hematological factors in acutely ill patients [58–60].

Patients may be allowed to bring their personal glucometer device to the hospital, but personal meters should not be used for documentation or treatment of inpatient hyperglycemia [15]. Hospital glucometers should be used to obtain POCT results and subsequently log them into the electronic health record to allow evaluation of individual and hospital-wide trends and patterns of inpatient glycemic control [15, 61]. Real-time continuous glucose monitoring (CGM) provides frequent measurement of interstitial glucose levels as well as direction and magnitude of glucose trends [32]. Recent studies have shown that CGM provides accurate estimation of BG levels in the hospital [62, 63] and may be more effective in detecting hypoglycemic episodes [62–64]. Despite its demonstrated advantages over POCT for inpatient glycemic monitoring, CGM has not yet received full FDA approval for inpatient use. However, the FDA did grant breakthrough device designation to DexCom in March 2022 for the use of its CGM devices in the hospital setting [65]. This designation provides a more efficient and streamlined review pathway so CGM technology can hopefully get to the hospital market faster. Notably, some hospitals with established glucose management teams already allow CGM use in selected patients on an individual basis (provided both the patient and the glucose management team are well-educated in the use of this technology [32]).

Glycemic Target Values

For the majority of non-critically ill patients treated with SC insulin, a target glucose range of 140–180 mg/dL (7.8 mmol/L) is recommended [32]. Guidelines also recommend that these targets should be modified according to clinical status [1, 15]. Glucose concentrations between 180 and 250 mg/dL (10–13.9 mmol/L) may be acceptable in patients with severe comorbidities and in inpatient care settings where frequent glucose monitoring or close nursing supervision is not feasible [32]. Glycemic levels >250 mg/dL (13.9 mmol/L) may be acceptable in terminally ill patients with short life expectancy. In such patients, less aggressive insulin regimens to minimize glucosuria, dehydration, and electrolyte disturbances are often more appropriate [32].

Consideration should be given to reassessing the insulin regimen if BG levels are consistently <100 mg/dL (5.6 mmol/L) [1, 15]. For avoidance of hypoglycemia (BG <70 mg/dL), the total basal and prandial insulin doses should be reduced if BG levels are consistently between 70 and 100 mg/dL (3.9–5.6 mmol/L) [15]. Modification of the treatment regimen is necessary when BG values fall <70 mg/dL (3.9 mmol/L) [1].

Approach to Management

As previously discussed, inpatient hyperglycemia is best managed with insulin therapy. The preferred insulin regimen for inpatient glycemic control of non-critically ill patients includes two different insulin preparations administered SC as BPP therapy [15]. The basal component requires administration of an intermediate- or long-acting insulin once or twice daily [15]. The bolus component consists of a short- or rapid-acting insulin given in conjunction with meals or nutrient delivery [15]. The safety and efficacy of BPP insulin regimens in non-critically ill patients have been demonstrated in numerous studies [44, 45, 66–68]. Correctional insulin refers to the administration of supplemental doses of short- or rapid-acting insulin together with the usual dose of bolus insulin for BG values above the target range and is usually customized to match the insulin sensitivity of each patient [15]. Table 46.1 provides examples of BPP insulin regimens along with correctional dose protocols for glycemic control in non-critically ill inpatients.

Adjustment of scheduled BPP insulin dosing can be based on total doses of correctional insulin administered in the previous 24 h [15, 45, 66]. When correctional insulin is required before most meals, it is usually the basal insulin component that should be titrated upward [15]. If BG remains consistently elevated at one time point, the dose of prandial insulin preceding that measurement should be increased [15, 43, 69]. For example, if the premeal BG at lunch is persistently elevated, it should be the breakfast dose of prandial insulin that is titrated upward. Appropriate inpatient glycemic control for many patients will often require daily insulin adjustment to reach glycemic targets while simultaneously avoiding hypoglycemia.

In patients who are NPO or unable to eat, bolus insulin should be held until nutritional intake is resumed. Basal insulin should be continued once daily (glargine or detemir) or twice daily (detemir or neutral protamine Hagedorn

[NPH]) [15]. Correctional doses of a rapid-acting insulin analog (e.g., aspart, lispro, etc.) or regular insulin can be given every 4–6 h as needed to treat BG above the desired range [15].

Medical nutrition therapy (MNT) should also be included as an essential component of any inpatient glycemic control program [15]. MNT is defined as the process of nutritional assessment and individualized meal planning in consultation with a nutrition professional [15, 70]. The goals of inpatient MNT include optimizing glycemic control, providing adequate calories to balance metabolic demands, and creating a discharge plan for follow-up care [15, 17, 32, 70–73]. Lack of attention to MNT in the hospital has been shown to contribute to unfavorable changes in BG [15, 29, 54, 74].

Many variables during hospitalization (e.g., abrupt discontinuation of meals in preparation for procedures or diagnostic studies, variability in meal intake due to acute illness, limitations in food choices, and poor coordination between insulin administration and meal delivery) can complicate nutritional management and create difficulties in predicting the efficacy of glycemic control strategies [15, 54]. Consistent carbohydrate (CHO) meal plans, in combination with MNT, may help facilitate inpatient glycemic control and negate some of these variables [15, 17, 32, 54]. Consistent CHO meal plans are preferred by many hospitals as they facilitate matching the prandial insulin dose to the amount of CHO consumed [32, 54] and may contribute to reductions in hypoglycemia [17, 71]. Current standards of care also recommend that if CHO counting is provided by the hospital kitchen, this option should be used in patients counting CHO at home [32, 75].

Successful inpatient glycemic control of non-critically ill patients requires a multifactorial approach that includes recognition of appropriate glycemic monitoring practices and target values along with institution of BPP insulin and MNT. Table 46.2 summarizes the procedures and strategies that should be employed to help achieve appropriate glycemic control in this patient population.

Table 46.2 Appropriate strategies for successful inpatient glycemic control in various patient populations

Patient population	Glycemic monitoring	Glycemic targets	Insulin regimen
Non-critically ill	• POCT FSG before meals and at bedtime if eating regular meals	• BG levels should generally be maintained between 140 and 180 mg/dL	• Scheduled subcutaneous basal plus prandial insulin therapy (see Table 46.1 for further details):
	• POCT FSG every 4–6 h in patients who are NPO or receiving continuous EN or PN	• Higher glycemic targets are acceptable in those who are terminally ill or have severe comorbidities	– Intermediate- or long-acting insulin (e.g., glargine, detemir, or NPH) given once or twice daily as basal component
	• More frequent POCT FSG may be considered for patients who experience or have increased risk for hypoglycemia		– Rapid-acting insulin (e.g., aspart or lispro) given in conjunction with meals as bolus component
			– Correctional doses of rapid-acting insulin given supplementally with the usual dose of bolus insulin for premeal BG values above target
Critically ill	• Patients whose severity of illness justifies invasive vascular monitoring:	• BG levels should be maintained between 140 and 180 mg/dL	• IV insulin infusion should be administered by means of validated written or computerized protocols
	– All blood samples should be drawn from an arterial line	• BG levels <110 mg/dL are not recommended and should be avoided	• Once clinically improved and/or eating regular meals, IV insulin infusion should be transitioned to SC insulin therapy (see Table 46.3 for further details)
	– If an arterial line is unavailable, sample from a venous line		
	– POCT FSG can be inaccurate and should be avoided, if possible		
	• Patients whose severity of illness does not justify invasive vascular monitoring:		
	– POCT FSG is appropriate		

(continued)

Table 46.2 (continued)

Patient population	Glycemic monitoring	Glycemic targets	Insulin regimen
Perioperative	• Determine the level of glycemic control during preoperative evaluation by checking hemoglobin A1c in patients with diabetes	• Premeal BG targets <140 mg/dL in conjunction with random BG targets <180 mg/dL in preoperative and postoperative patients who are eating regular meals	• In ambulatory patients undergoing relatively short procedures, BPP insulin therapy should be used
	• In stable patients undergoing relatively short outpatient procedures, check BG on admission, before procedure, and at discharge	• Intraoperative BG levels should be maintained between 100 and 180 mg/dL	• The day of surgery, use 75–100% of daily long-acting insulin (glargine or detemir) dose
	• For longer outpatient procedures or patients receiving intraoperative subcutaneous insulin, BG should be monitored every 1–2 h	• If a patient must be monitored in a surgical ICU post-procedure, BG should be maintained between 140 and 180 mg/dL	• Prandial insulin should be withheld while a patient is fasting
	• For extensive surgical procedures or patients receiving intravenous insulin infusion, BG should be monitored every 30 min		• Once the patient resumes eating regular meals, full BPP regimen can be resumed
			• IV insulin therapy is appropriate for patients undergoing long, extensive surgical procedures or those who will need to be monitored in an ICU setting post-procedure

POCT point-of-care testing, *IV* intravenous, *SC* subcutaneous, *FSG* fingerstick glucose, *ICU* intensive care unit, *EN* enteral nutrition, *BPP* basal plus prandial, *PN* parenteral nutrition, *BG* blood glucose, *NPH* neutral protamine Hagedorn

Table 46.3 Transitioning from intravenous to subcutaneous insulin in the patient who is eating regular meals

	Time (h)								
Patient data	0000	0100	0200	0300	0400	0500	0600	0700	0800
IV insulin infusion rate (units/h)	2.2	2.2	2.1	2.0	2.0	2.0	1.9	1.8	1.8
Blood glucose (mg/dL)	148	143	145	141	137	139	135	133	131

The above data demonstrates both good glycemic control and relatively stable insulin infusion rates. To calculate subcutaneous basal plus bolus insulin doses, follow these steps

1. Calculate the 24-h intravenous insulin requirement
   (a) In the example above, the patient has an average insulin infusion rate of 2 units/h
   (b) Calculated 24-h intravenous insulin requirement: 2 units/h × 24 h = 48 units
2. Calculate the subcutaneous basal insulin dose
   (a) Most sources [1, 76] recommend using 80% of the 24-h intravenous insulin requirement as the subcutaneous basal insulin dose
   (b) 80% of 48 units = 38 units
   (c) As this was calculated from an overnight period of time while the patient was not eating, the dose can be administered as 38 units of basal insulin once daily
3. Calculate the subcutaneous bolus (prandial) insulin dose using a weight-based calculation
   (a) Given the possibility of decreased appetite, starting with a conservative estimate of 0.2 units/kg for total prandial dose is appropriate
   (b) 0.2 units/kg × 80 kg = 16 units and 16 units/3 meals = approximately 5 units per meal
4. Final orders
   (a) 38 units subcutaneous daily (insulin glargine/detemir)
   (b) 5 units subcutaneous three times daily with meals (insulin lispro/aspart/glulisine)

Adapted with permission from Reference [77]

[a] The patient weighs 80 kg; data extracted from an overnight period of time when the patient is not eating

Glycemic Control of the Critically Ill Patient

Hyperglycemia is common in critically ill patients, including those without a known history of DM [78]. Patients receiving treatment for critical illness develop hyperglycemia due to the effects of endogenous stress responses and the by-products of medical interventions [78]. Inflammatory cytokines and stress hormones, such as epinephrine and cortisol, inhibit insulin release and promote insulin resistance, functionally increasing BG levels by stimulating gluconeogenesis and glycogenolysis while impeding glucose uptake in peripheral tissues [78–80]. Many medical therapies utilized in the treatment of critically ill patients also promote hyperglycemia, including administration of exogenous catecholamines and glucocorticoids, infusion of dextrose for parenteral nutrition, and even bedrest itself, which may impair glucose uptake in skeletal muscles [78, 81, 82]. In the past two decades, glycemic control among critically ill patients has been a topic of extensive study, leading to many changes in clinical practice [83].

Glycemic Monitoring

Measurement of BG concentration in critical care settings is often performed in intermittent fashion, with analysis using either POCT glucometers, laboratory blood draws, or blood gas analyzers [83]. The accuracy of glucometers has been the subject of numerous studies, with the majority concluding that they are insufficiently accurate for exclusive evaluation of BG values in the ICU [58, 83–86]. Many current glucometers are susceptible to interference from reducing substances such as ascorbic acid and acetaminophen (paracetamol), and accuracy is also affected by a patient's hematocrit levels [57, 83, 87]. The effect of hematocrit is particularly concerning in the ICU, where levels can fluctuate for many reasons. One study has demonstrated that a patient with a true BG of 80 mg/dL and a hematocrit of 0.25 may have a positive bias as great as 18 mg/dL [83, 87]. Another consideration is that BG concentration varies in different vascular beds and the site from which blood is sampled may introduce errors [83]. Sampling capillary blood in ICU patients, particularly those who are hemodynamically unstable and treated with vasopressors, can introduce large errors when compared to a reference method in which BG is measured from central venous or arterial draws [83, 84, 88]. Sampling from indwelling arterial or venous catheters in ICU patients is a reasonable option that is preferable to venipuncture, given the frequency with which BG is measured in the ICU [83].

Alternatives to the use of glucometers are measurements in the hospital's central laboratory or using a blood gas analyzer in the ICU [83]. Although central laboratory measurement is more accurate, the time delay in obtaining results makes this a less-than-ideal option in most ICU settings [83]. Using a blood gas analyzer to measure BG concentration is a practical solution but may have considerable cost implications [83]. Measurements from a properly maintained blood gas analyzer will have similar accuracy to central laboratory measurements [83, 84].

Current guidelines for BG measurement in the ICU recommend that all patients whose severity of illness justifies the presence of invasive vascular monitoring (i.e., indwelling arterial and/or central venous catheter) should have samples for measurement taken from the arterial catheter as the primary option [83]. If an arterial catheter is temporarily or permanently unavailable, blood may be sampled from a venous catheter as a secondary option (appropriate attention should be paid to maintaining sterility and avoiding contamination of the sample by flush solution in this scenario) [83]. When a patient's severity of illness does not require the presence of invasive vascular monitoring, POCT capillary BG samples obtained via glucometer are acceptable [83].

Although intermittent BG measurement is the current standard practice for critically ill patients, CGM holds great promise in this patient population. Potential advantages of CGM include the ability to observe trends in BG concentration and intervene before values enter an unacceptable range and removal of error both in timing of BG measurements and in sampling and analysis of blood [83]. Primary concerns with CGM use in the ICU relate to the effects of hemodynamic changes, pressor use, and potential interfering medications [89]. At this time, more data are needed before recommendations either for or against CGM use in critically ill patients can be made. A recent real-world preliminary analysis of the accuracy of CGM compared to POCT in 11 ICU patients with confirmed coronavirus disease 2019 (COVID-19) demonstrated early feasibility, considerable accuracy, and meaningful reduction in the frequency of point-of-care glucose testing [90]. Larger studies are needed to confirm these findings.

Glycemic Target Values

Current BG target values for critically ill patients are primarily based on results from the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, a multicenter and multinational randomized controlled trial that tested the effect of tight glycemic control on outcomes among 6104 critically ill patients, the majority of whom (>95%) required mechanical ventilation [1, 91]. In this study, patients were randomized to intensive or conventional insulin therapy group. The glycemic target range was 81–108 mg/dL in the intensive insulin therapy group, while target BG was ≤180 mg/dL in the conventional insulin therapy group (with insulin administration reduced and then discontinued if BG levels fell below 144 mg/dL [84]). Both 90-day mortality (78 more deaths; 27.5% vs. 24.9%; $p = 0.02$) and rates of severe hypoglycemia (6.8% vs. 0.5%; $p = <0.001$) were significantly higher in the intensive versus conventional group [91]. Subsequently, several randomized controlled trials evaluating intensive insulin therapy among mechanically ventilated neurologic patients [92], patients with traumatic brain injuries [93], and critically ill pediatric patients [94] have all failed to demonstrate a clinical benefit to tight glycemic control in ICU patients [83]. Based on these findings, current guidelines for glycemic targets in critically ill patients on IV insulin therapy recommend that BG should be maintained between 140 and 180 mg/dL (7.8 and 10 mmol/L), with greater benefit potentially realized at the lower end of this range [1]. Somewhat lower glycemic targets may be appropriate in select patients, but strong evidence is currently lacking and prevents such a recommendation [1]. Targets <110 mg/dL (6.1 mmol/L) are not recommended and should be avoided [1].

Approach to Management

In the ICU setting, continuous IV insulin infusion is the most effective therapy for achieving recommended glycemic tar-

gets [17, 32]. Due to the short half-life of circulating insulin, IV delivery allows for rapid dosing adjustments to address alterations in clinical status [1]. Current guidelines recommend that IV insulin should be administered based on validated written or computerized protocols that allow for predefined adjustments in the infusion rate, accounting for glycemic fluctuations and insulin dose [32]. Several examples of published protocols are available for review [95–98]. Continued education of healthcare staff along with ongoing review of patient data and protocol results is critical for successful implementation of any insulin protocol [1, 95–98]. Table 46.2 summarizes appropriate strategies for successful inpatient glycemic control in critically ill patients.

Critically ill patients receiving IV insulin therapy will typically require transition to SC insulin once they begin eating regular meals or have clinically improved enough to be transferred to lower intensity care [1]. A safe transition requires appropriate planning and must be carried out systematically. SC basal insulin must be given at least 2–4 h prior to discontinuation of IV insulin therapy to prevent rebound hyperglycemia [76, 77]. There are currently no consensus guidelines for transitioning from IV to SC therapy, but typically 75–80% of the total daily IV infusion dose is proportionally divided into basal and prandial components [1]. The safest method is to find a several-hour period of time during which BG values are at goal and IV insulin rates are not particularly elevated or variable (i.e., the rate is reasonable and stable) [77]. The healthcare provider can then look at infusion rates during this stable period of time (ideally 6–8 h in length [99]) and extrapolate these data into a 24-h time period [77]. Utilizing this method allows for a reasonable calculation of the patient's 24-h IV insulin utilization [77]. Table 46.3 provides an example of calculating the insulin regimen necessary to transition a patient from IV to SC insulin therapy.

Glycemic Control of the Perioperative Patient

Patients with DM are more likely to undergo surgery than patients without DM [17, 44]. Surgery in DM patients is associated with longer length of hospitalization, greater perioperative morbidity and mortality, and increased rates of perioperative complications and healthcare resource utilization than in patients without DM [17, 44, 100, 101]. One retrospective observational study of 409 cardiac surgical patients demonstrated that intraoperative hyperglycemia was an independent risk factor for perioperative complications (including mortality) after adjusting for postoperative BG concentrations [102, 103]. The authors of this study also indicated that each 20 mg/dL (1.1 mmol/L) increase in BG concentration above 100 mg/dL (5.6 mmol/L) during surgery was associated with a 34% increased likelihood of postoperative complications [102]. Another retrospective cohort study of infra-inguinal vascular surgery patients showed that the rise in BG was proportional to an increased frequency of postoperative infections [104].

Surgical patient populations pose many unique challenges to clinicians. Despite the increased risk of perioperative complications, hyperglycemia is frequently overlooked and inadequately addressed [29, 44]. Given the growing evidence linking perioperative hyperglycemia to many poor outcomes, it is imperative that healthcare providers identify and proactively address this issue.

Glycemic Monitoring

Preoperative identification of patients with DM and those at risk for perioperative dysglycemia provides a potential opportunity to reduce morbidity and mortality [105]. However, it should be noted that the incidence of preoperative hyperglycemia might not be entirely due to DM. For example, a prospective study of 493 non-DM patients undergoing elective, non-cardiac surgery found that 25% had elevated fasting plasma glucose the morning of surgery [106].

Glycemic monitoring approaches for perioperative patients are similar to those used for non-critically ill and critically ill patients, depending upon the type and length of surgery performed [103] and whether the patient is monitored in the surgical ICU, general surgical floor, or discharged home after the procedure is completed. General recommendations include determining the level of glycemic control during the preoperative evaluation by checking HbA1c values [103]. Elevated HbA1c, as a marker of poor glycemic control, correlates with increased perioperative risk in DM patients [102]. Further recommendations include checking BG levels on the patient's arrival before surgery and prior to discharge home [103]. The recommended frequency of intraoperative BG monitoring depends on many factors. In metabolically stable DM patients undergoing relatively short (i.e., less than 2 h) outpatient procedures, it is only necessary to check BG on admission, before operation, and at discharge [105]. For longer outpatient procedures or for patients receiving intraoperative SC insulin, BG should be monitored every 1–2 h at minimum [103, 105]. For higher-acuity patients undergoing extensive surgical procedures or those on intraoperative insulin infusion therapy, the American Diabetes Association recommends BG monitoring as frequently as every 30 min [32]. If the patient is observed in the hospital after the procedure, POCT is an appropriate monitoring method unless the patient is in the ICU. Once the patient is eating regular meals, recommendations for glycemic monitoring mirror those for non-critically ill patients.

Glycemic Target Values

BG goals for preoperative and postoperative patients who are eating regular meals are similar to those of non-critically ill

patients and generally target values between 140 (7.8 mmol/L) and 180 mg/dL (10 mmol/L), as long as these targets can be safely achieved [1, 15]. Intraoperative BG levels should be maintained between 100 and 180 mg/dL (6–10 mmol/L), with appropriate steps taken to prevent intraoperative hypoglycemia [103, 106]. If a patient must be monitored in a surgical ICU post-procedure, glucose should be maintained between 140 and 180 mg/dL (7.8 and 10 mmol/L) [1].

Approach to Preoperative Management

Healthcare providers should have a detailed understanding of the patient's history of disease, including specific diagnosis (T1DM, T2DM, gestational DM, etc.), duration of disease, current treatment regimen, adequacy of control, and the presence and/or severity of any comorbidities [104]. Persons with DM admitted for surgical procedures should generally have their home oral antidiabetic medications discontinued [9], and it is reasonable to stop most of these medications on the morning of surgery [107, 108]. However, SGLT2 inhibitors require special attention given that the FDA now recommends that these agents should be stopped 3 days before scheduled surgeries (4 days in the case of ertugliflozin) [32] due to a higher risk of ketoacidosis. All patients with a known history of DM should be thoroughly evaluated before entering the operating room to aid in creating a successful perioperative treatment regimen. Postponing surgery in patients who present on the morning of procedure with significant dehydration, ketoacidosis, and/or hyperosmolar nonketotic states is recommended [103]. Table 46.2 summarizes recommendations for achieving appropriate inpatient glycemic control in perioperative patients.

Consensus guidelines recognize IV insulin therapy as the best method for controlling hyperglycemia in critically ill and non-critically ill surgical patients [1]; however, many logistical difficulties limit the use of this therapy in most hospital settings (particularly in non-ICU patient populations [103]). For ambulatory patients undergoing relatively short procedures, the preferable method for perioperative glycemic control is SC BPP insulin therapy. When SC insulin is continued in patients who are fasting, adjustment of their long-acting basal insulin dose is often not necessary, provided they have been receiving an adequate dose prior to admission [103, 109]. Specific recommendations include avoiding alterations of basal insulin the day before surgery unless there is report of hypoglycemia or the patient is on a diet restriction in the preoperative period [103]. On the day of surgery, use 75–100% of daily long-acting insulin dose [103]. If NPH is being used as the basal insulin, the evening dose should be reduced to 75% the day before surgery, and 50–75% of the usual morning dose should be given the day of surgery [103]. Prandial (bolus) insulin should be withheld while a patient is fasting [103]. The use of basal insulin in combination with correctional insulin can be effective at maintaining glycemic control in the desired range with low risk of hypoglycemia [44]. Once a patient is eating regular meals and monitored in a non-ICU setting, a BPP insulin regimen can be fully resumed. IV insulin therapy is appropriate for patients undergoing long, extensive surgical procedures or those who will need to be monitored in an ICU setting post-procedure [103]. IV insulin has the advantage of being quickly titratable with a rapid onset of action [105], allowing for precise glycemic control in the perioperative period. For patients treated with IV infusions, it is important to safely transition to SC insulin while maintaining glycemic control as patients transfer across different hospital units [103]. Table 46.3 details methods for converting IV therapy to an appropriate SC insulin regimen.

Special Considerations

Many special circumstances are encountered during routine inpatient care of DM patients. Not all patients are able to tolerate regular PO intake and may require EN or PN, and the approach to glycemic control of such patients is a little different than other management strategies previously described. Other special circumstances include patients who are admitted with insulin pumps and those who experience glucocorticoid-induced DM while hospitalized.

Enteral and Parenteral Nutrition

Malnutrition is reported in up to 40% of critically ill patients [75] and is associated with many poor outcomes, including increased risk of hospital complications, higher mortality rates, longer length of hospitalization, and increased healthcare costs [15, 110]. Improving the nutritional state is an important goal of inpatient care for malnourished patients; unfortunately, not all patients are able to tolerate PO intake and require EN or PN therapy. There are several retrospective and prospective studies demonstrating that the use of EN or PN therapy is an independent risk factor for the onset or aggravation of hyperglycemia independent of a prior history of DM [15, 78, 111, 112]. Early intervention to prevent and correct hyperglycemia in these patients may improve clinical outcomes [15]; however, achieving desired glycemic goals in this population poses many unique challenges [68, 78]. Current recommendations include initiating POCT in patients with or without a history of DM receiving PN or EN [15]. Several different management strategies utilizing SC insulin have been suggested, and recommendations vary by whether the patient is receiving PN or intermittent, continuous, or cycled EN [15]. For those receiving continuous EN, recommendations include administering basal insulin once (if glargine) or twice (if NPH or detemir) daily in combination with a short- or rapid-acting insulin analog in divided doses every 4 (if lispro, aspart, etc.) to 6 (if regular insulin)

hours [15]. For patients on cycled EN, guidelines recommend administering basal insulin in combination with a short- or rapid-acting insulin analog upon the initiation of EN [15]. Repeating the dose of rapid-acting insulin at 4-h intervals or short-acting insulin at 6-h intervals for the duration of EN therapy is also recommended [15]. It is also preferable to give the last dose of rapid-acting insulin approximately 4 h before and short-acting insulin approximately 6 h before discontinuation of EN [15]. For those receiving bolus EN, administer short-acting or rapid-acting insulin before each bolus is delivered [15]. Finally, for patients receiving PN, regular insulin administered as part of the PN formulation can be both safe and effective [15]. Subcutaneous correctional dose insulin can be utilized in addition to the insulin that is mixed with the PN to correct any hyperglycemic excursions that may occur [15].

Glucocorticoid Therapy

Hyperglycemia is a common complication of glucocorticoid therapy, with several studies demonstrating a prevalence between 20% and 50% among patients without a previous history of DM [56, 113]. Glucocorticoid therapy increases hepatic glucose production, impairs glucose uptake in peripheral tissues, and stimulates protein catabolism with resulting increased concentrations of circulating amino acids, thus providing precursors for gluconeogenesis [114–116]. It is generally accepted that these physiological changes ultimately exacerbate postprandial hyperglycemia [117]; thus, all patients treated with glucocorticoid therapy should be evaluated for hyperglycemia whether they have a known history of DM or not. Current recommendations include initiating bedside POCT in any patient receiving treatment with glucocorticoids [15]. POCT can be discontinued in persons without DM if all BG results are <140 mg/dL (7.8 mmol/L) without insulin therapy for a period of 24–48 h [15]. Insulin therapy should be initiated in patients demonstrating persistent hyperglycemia [15]. The majority of patients with steroid-induced hyperglycemia can be treated with SC BPP regimens to achieve glycemic control, with the insulin regimen based on a starting dose of 0.3–0.5 units/kg/day [15]. Adjustment of insulin doses is often required when the glucocorticoid dose is changed [15]. During glucocorticoid tapers, insulin dosing should be proactively adjusted to avoid hypoglycemia [1].

Insulin Pumps

Patients treated with continuous subcutaneous insulin infusion (i.e., insulin pump) therapy in the outpatient setting require unique attention when hospitalized. With increasing utilization of pump therapy, many institutions allow patients on insulin pumps to continue using these devices in the hospital. Patients who utilize pump therapy in the outpatient setting can be considered for diabetes self-management while hospitalized, provided they have the mental and physical capacity to do so [1, 17, 118, 119]. In this scenario, nursing personnel should document basal rates and bolus doses (at least daily) [1]. The availability of hospital personnel with expertise in pump therapy is also vital [118, 119]. Clear policies and procedures should be established at the institutional level to guide the continued use of insulin pump technology in hospitalized patients [15].

Hypoglycemia

Hypoglycemia (both spontaneous and iatrogenic) is associated with higher risk of complications among hospitalized patients, including longer and more expensive hospital stays and increased mortality rates [120–122]. The risk for hypoglycemia is higher in hospitalized patients due to variability in insulin sensitivity related to the underlying illness, changes in counter-regulatory hormonal responses to procedures or illness, and interruptions in usual nutritional intake [123, 124]. Hospitalized patients who are elderly or severely ill are especially vulnerable to its adverse effects [120]. Given the negative outcomes associated with inpatient hypoglycemia, it is imperative that appropriate steps be taken to prevent and reduce episodes as much as possible.

Inpatient hypoglycemia is classically defined as any BG <70 mg/dL [122], as this level correlates with the initial threshold for the release of counter-regulatory hormones [15, 125, 126]. Insulin therapy is the most common preventable cause of iatrogenic hypoglycemia, followed by improper prescribing of other glucose-lowering medications, inappropriate management of the first episode of hypoglycemia, and nutrition-insulin mismatch (often related to an unexpected interruption of nutrition) [32].

For avoidance of hypoglycemia, consideration should be given to reassessing the insulin regimen if BG values <100 mg/dL are consistently noted. Modification of the regimen is necessary when BG values are <70 mg/dL, unless the event is easily explained by other factors such as a missed meal [1, 32]. Guidelines also suggest that a standardized hospital-wide, nurse-initiated hypoglycemia treatment protocol should be in place to immediately address any blood glucose <70 mg/dL (3.9 mmol/L) [32]. Additionally, the Joint Commission recommends that all hypoglycemic episodes be evaluated for a root cause and that such episodes be aggregated and reviewed to address any systemic issues [32, 127].

Emerging technologies focused on the prediction of inpatient hypoglycemia have recently been tested. While this work is in its infancy stages, early results are promising. Several groups have developed machine-learning predictive algorithms for inpatient hypoglycemia in both non-critical [128–131] and ICU [132] populations. Models like these are

potentially important and, once validated for general use and prospectively tested (ideally in randomized controlled clinical trials), could provide a valuable tool to reduce rates of hypoglycemia in hospitalized patients [32]. One study has even shown that a real-time predictive informatics-generated alert, when supported by trained nurse responders, significantly reduced severe hypoglycemia among patients hospitalized on acute care medical floors [133].

Transitioning from Hospital to Home

Preparation for transition to the outpatient setting is an important goal of inpatient diabetes management and begins with hospital admission [1]. Hospital discharge itself represents a critical time for ensuring a safe transition to the outpatient setting and reducing the need for emergency department visits and rehospitalization [15], and poor coordination of patient care at the time of discharge is associated with medical errors and readmission [134]. Successful coordination of this transition requires a team approach that includes physicians, nurses, dietitians, case managers, and social workers [17]. An outpatient follow-up visit with the primary care provider, endocrinologist, or diabetes care and education specialist within 1 month of discharge is advised for all patients experiencing hyperglycemia while hospitalized [32]. If glycemic medications are changed or glycemic control is not optimal at discharge, an earlier appointment (e.g., 1–2 weeks) is preferred, and frequent contact may be needed to avoid hyperglycemia and hypoglycemia [32]. For patients discharged home on insulin therapy as a new medication, it is important that patient education and written information be provided for method and timing of insulin doses and recognition and treatment of hypoglycemia [15, 135]. Initiation of insulin administration should be instituted at least 1 day before discharge to allow assessment of safety and efficacy [15]. Measurement of HbA1c during hospitalization can assist in tailoring the glycemic management of DM patients at discharge. For patients with acceptable preadmission glycemic control (i.e., HbA1c <7%), guidelines suggest reinstitution of their preadmission insulin regimen or oral and non-insulin injectable antidiabetic medications at discharge (if there are no contraindications to continued therapy [15]). Patients with elevated HbA1c often require intensification of the outpatient regimen at discharge [15].

Conclusion

Optimal glycemic control throughout hospitalization is a goal all healthcare providers should strive to achieve. Appropriate glycemic control during the hospital stay requires effort on many levels, including provider education to aid in ordering appropriate insulin regimens, nursing coordination on the timing of insulin administration and treatment of hypoglycemia, laboratory personnel measuring BG and reporting results promptly, and nutrition services assisting in dietary choices. Hospitals should take appropriate steps to achieve euglycemia and make patient safety in glycemic control a reality for all inpatients.

Multiple-Choice Questions

1. In the hospital, what blood glucose level is defined as representing hypoglycemia (values in mg/dL)?
   (a) <80
   (b) **<70**
   (c) <60
   (d) <50
   (e) <40
2. In the hospital, what blood glucose level is defined as representing hyperglycemia (values in mg/dL)
   (a) >100
   (b) >120
   (c) **>140**
   (d) >200
   (e) >250
3. In the hospital, what glucose range should be targeted for most patients?
   (a) 200–240
   (b) 160–200
   (c) **140–180**
   (d) 120–160
   (e) 100–140
4. Modification of the treatment regimen is necessary once any blood glucose value below what threshold is observed?
   (a) <80
   (b) **<70**
   (c) <60
   (d) <50
   (e) <40
5. Inpatient hyperglycemia is *best managed* with what form of therapy?
   (a) Metformin
   (b) Sulfonylureas
   (c) **Insulin**
   (d) GLP-1 agonists
   (e) SGLT2 inhibitors
6. In the ICU setting, what form of therapy has proven to be the *most effective* for achieving recommended glycemic targets?
   (a) Sliding scale insulin
   (b) Metformin
   (c) Sulfonylureas
   (d) **IV insulin infusion**
   (e) Basal insulin alone

7. If a patient is to initiate insulin therapy prior to hospital discharge, when should this be started to allow for assessment of safety and efficacy?
   (a) One week before discharge
   (b) After discharge
   (c) **At least 1 day before discharge**
8. What is the preferred method for blood glucose (BG) monitoring in the non-critically ill inpatient?
   (a) Continuous glucose monitoring
   (b) Venous BG sample
   (c) **Bedside capillary point-of-care testing (POCT)**
9. True or False: Patients being treated with glucocorticoid therapy should be evaluated for hyperglycemia, whether they have a known history of DM or not.
   (a) **True**
   (b) False
10. True or False: The accuracy of many glucometers can be altered by certain medications (e.g., acetaminophen [paracetamol]) and/or by a patient's hematocrit levels.
   (a) **True**
   (b) False

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Diabetes and Infection

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Atulya Atreja, Sanjay Kalra, and Joel Rodriguez-Saldana

Whether it be the plague or influenza,
one thing that we learn at the knee of our "alma mater"
is that diabetics are more likely to get it. (Larkin and colleagues [1])

Introduction

Before the discovery of insulin and antibiotics, it was estimated that infections were the cause of death of one in five diabetic patients [2]. Following the discovery of insulin, a decrease in mortality from sepsis and tuberculosis was documented since 1935 [3]; in the late 1960s, the estimated mortality from infections in people with diabetes was 5% [2]. Nevertheless, it has been shown that diabetes continues to increase the predisposition to infections, especially bacterial, fungal, and viral. Albeit not traditionally recognized, acute infections are among the ten leading clinical characteristics in patients with newly diagnosed type 2 diabetes [4]. For example, Drivsholm and colleagues reported that the prevalence of genital itching, balanitis in men, recurrent urinary tract and skin infections among 1137 Danish patients newly diagnosed with type 2 diabetes was 27.2%, 12.0%, 5.7%, and 4.3% [4]. Largely unperceived, the use and costs of antimicrobials in patients with diabetes are significantly higher in comparison with people without diabetes [5]. Using national registries from Finland, Reunanen et al. reported that over 1 year, 43.6% of patients used systemic antibacterials and 4.5% had used systemic antimycotics, in comparison with 29.1% and 1.9% respectively in people without diabetes [5]. Until the 1980s, controversy prevailed about the increased frequency of infections in patients with diabetes; many clinicians believed that people with diabetes had an increased susceptibility to infection, but this belief was not supported by strong evidence [1, 6, 7]. Contributing factors increasing the risk of infections in patients with diabetes include comorbidities and chronic complications such as foot ulcers and neurogenic bladder [6]. Beyond a disturbance of glucose metabolism, diabetes is an inflammatory disease in which chronic complications, including neuropathy, chronic vascular and renal diseases alter the response to pathogens [8].

Magnitude of Risk

The relevance of infections in the morbidity and mortality of people with diabetes has been neglected, is not addressed or reported in clinical trials, and is not recognized in clinical guidelines for diabetes management [9]. Nevertheless, infections impair quality of life and impose short-time and long-time threats on the life of people with diabetes. Despite the general belief investigations about the epidemiology of infections in people with diabetes are scarce [9].

The landmark specific studies—three retrospective and three longitudinal—were carried out in Canada, Netherlands, England, South Korea, and the United States [7, 10–14]. In the first retrospective trial, risk ratios of infections and death attributable to infectious disease were compared in two groups of 513,749 non-diabetic and diabetic patients [7]. The risk ratio for infections was equal in both groups, but the risk ratio for infectious-related hospitalization was 2.1 and the risk ratio for death attributable to infection was 1.92 in patients with diabetes [7]. Risk ratios for infectious disease hospitalization or physician claims for infectious disease were higher in patients with diabetes; almost half of the patients with diabetes had at least one hospitalization or physician claim [7]. In 2018, Carey, Critchley et al. published two reports from the retrospective analysis of 102,493 pri-

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mary care patients with type 1 and type 2 diabetes aged 40–89 years [10, 11]. After 5 years of follow-up, 55.0% of patients with type 1 diabetes and 56.9% of patients with type 2 diabetes had at least one infection compared with 41.3% and 46.2% of control subjects respectively [10]. They reported clear trends for increasing risk of infection at poorer levels of glycemic control and that the long-term risk of skin, cellulitis, candidiasis, bone and joint infections, endocarditis, and sepsis tended to rise at higher HbA1c levels, albeit some infections showed elevated rates among patients with diabetes with HbA1c <6.0%. In other words, even patients with good glycemic control were at higher risk of infections than people without diabetes [11]. Patients with diabetes were three times as likely to be hospitalized for infection, especially those with type 1 diabetes who were also at higher risk of death [11].

Prospective studies about the risk of infection among patients with diabetes include one of 12-month duration in which 7417 adult patients with type 1 (N = 705) or type 2 (N = 6712) diabetes were compared with 18,911 patients with hypertension [12]. Patients with diabetes had higher risks of lower respiratory tract infections, urinary tract infection, bacterial and skin and mucous membrane infection, and mycotic skin and mucous membrane infection [12]. Adjusted odds ratios were higher in every category for patients with type 1 diabetes, and the risk increased with recurrences of common infections [12]. The second study comprised a cohort of 66,426 diabetes and 132,852 age-sex-region matched non-diabetes control from the general population in South Korea [13]. Compared to non-diabetes controls, people with diabetes had a higher risk of almost all types of infections with higher adjusted incidence rate ratios for hepatic abscess, central nervous system, skin and soft tissue infections [13]. Patients with diabetes were at higher risk to intensive care unit admission and death than the general population [13]. Last but not least, Fang and colleagues conducted a 30–32-year prospective cohort analysis to investigate hospitalization for infection among 12,379 patients with diabetes, from which in 4229 infection was the cause of admission [14]. After adjusting for potential confounders, people with diabetes had a higher risk for infection (HR 1.67), especially pronounced for foot infection (HR 5.99). Overall infection mortality was low in this study (8.5%), but the adjusted risk was increased in people with diabetes (HR 1.72) [14].

Pathogenesis

The search for "an intrinsic problem" to explain the association of diabetes and infection goes back to Lassar, who postulated in 1904 that organisms thrive in a high sugar medium [1]. In 1938 Marble and colleagues stated that "patients with diabetes have less resistance to infection than normal individuals is a fact met with in the everyday experience of the clinician" and admitted that the lessened ability to cope with infection was undeniable prior to the introduction of insulin and (even) afterwards in patients with poor glycemic control [15]. In this pioneering report, Marble et al. suggested various factors as the cause of the lower resistance to infection in people with diabetes, some of which have been confirmed over the years: (1) increased sugar content of blood and tissues, (2) decreased activity of blood elements associated with resistance to infection, (3) inadequate functioning of fixed tissue cells, (4) lower capacity of tissue to react to antigenic stimuli, (5) undernutrition [15].

Diabetes and infection exemplify a vicious circle: insulin resistance and beta cell failure impair the immune response, and increased susceptibility to infections precipitates metabolic complications in patients with diabetes. Acute infections impair glycemic control, and infection is an important cause of hyperglycemic crisis, including ketoacidosis and non-hyperglycemic hyperosmolar state [16]. Large population-based observational studies have reported strong associations between higher HbA1c levels and infection risks for patients with Type 1 and Type 2 Diabetes [9]. A recent review identified 13 studies in which infections could be associated with glycemic control [8]. Except for the Diabetes Control and Complications Trial (DCCT), all the studies discussed in this review were observational either cohort or case control, identifying associations but not clearly causality [9]. Importantly, all were carried out in high income countries, but associations between diabetes and infection could be also important (and higher) in low and middle resource countries, where diabetes prevalence is rising most rapidly, and glucose control is lower [9]. Despite their limitations to measure the impact of diabetes on infection, it has been shown that hyperglycemia has negative effects on the outcomes in people with diabetes. Glycemic control is an essential goal to reduce the risk of infections and to protect maintenance of normal host defense mechanisms that determine resistance and response to infection [16]. In support of this statement, Burekovic et al. studied 450 patients with diabetes hospitalized in an intensive care unit from Bosnia and Herzegovina and they found a positive correlation between HbA1c, C-reactive protein, and HbA1c levels with acute infections [17].

The Immune Response

Specific defects in innate and adaptive immune function in people with type 1 and type 2 diabetes have been identified in multiple studies [2]. Reported abnormalities include an increase in inflammatory markers (tumor necrosis factor, interleukin-6, C-reactive protein, plasminogen activator inhibitor) and ineffective functioning of T lymphocytes, neu-

Table 47.1 Pathogenic mechanisms of infection in patients with diabetes [2, 6, 8, 9, 15–26]

Mechanism	Disorder
Leukocyte count	Increased, larger and granular; diminished levels of antioxidant genes, increased levels of proapoptotic and proinflammatory genes
Innate immunity	Macrophage dysfunction: reduced phagocytosis
	Defects in pathogen recognition; impairment in the number and activity of dendritic (antigen-presenting) cells: higher susceptibility to opportunistic infections
	Disorders in pathogen elimination, including: (1) polymorphonuclear adhesion to vascular endothelium, (2) transmigration through the vessel wall down a chemotactic gradient, (3) phagocytosis and microbial killing
	Neutrophil dysfunction including: (1) decreased phagocytosis, (2) diminished respiratory burst capacity and degranulation, (3) glucose-dependent reduction in superoxide production, (4) reduced monocyte proliferation, (4) reduced bactericidal capacity, (5) delayed bacterial clearance, (6) increased severity of infections, (7) higher susceptibility to infections, (8) apoptosis
	Downregulation of Toll-like receptors: phagocyte inhibition and killing of *Staphylococcus aureus*
	Vascular dysfunction, including (1) upregulation of intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1 and selectin, resulting in limited chemotactic migration out of vessels at sites of inflammation, (2) reduced endothelial-dependent relaxation, (3) blunted nitric oxide response to bradykinin, (4) dysregulation of nitric oxide production and release of prostanoids with resulting vasoconstriction, (5) increased endothelial permeability, tissue edema
	Disorders in the complement cascade, including (1) impairment in the lectin pathway, (2) reduced attachment of C-type lectin proteins, (3) upregulation of C3 and C4 gene expression, chronic inflammatory state, (4) inhibition of complement receptor and Fc gamma receptor, (5) reduced opsonization and phagocytosis of microorganisms
	Disturbances in cell signaling pathways, activation of mitogen-activated protein kinases, including nuclear factor-kB and protein kinase C
	Non-enzymatic glycosylation of immunoglobulins
	Bacterial biofilm formation, increased survival of microorganisms
Adaptive immunity	Specific defects in T lymphocyte function
	Glycosylation and impaired functioning of antibodies in proportion to HbA1c levels
	Paradoxical hyper-reactive antigen-specific T cell inflammatory response
	Impairment in cytokine function and reduced synthesis: high levels of single and double cytokine CD4+ Th1 cells
	High levels of type 1 (tumor necrosis factor-α, IFN-γ, interleukin-2), type 2 (interleukin-5), type 17 (interleukin-17 cytokines) and other proinflammatory cytokines (interleukin-1β, interleukin-6, interleukin-18, C-reactive protein), and an anti-inflammatory cytokine (interleukin-10): oxidative stress and insulin resistance
	Low levels of IL-22
	Decreased frequency and function of natural Treg cells
	Enhanced frequencies of central memory CD4+ and CD8+ T cells resulting in disturbances on central memory, effector memory, and naïve T cells
	Diminished expression of cytotoxic markers Perforin, Granzyme B, and CD107a, decreased antigen-stimulated CD8+ T cell cytotoxic activity
	NK cell dysfunction: reduction in natural killer (NK) receptor NKG2D
	Higher levels of tissue damage in diabetic patients with tuberculosis

trophils, oxidant-antioxidant imbalance, and deficient opsonophagocytosis [18–25]. These infections are often difficult to evaluate and eradicate due to reduced humoral immune responses. Host factors like microvascular and macrovascular insufficiency, sensory and autonomic neuropathy, and mucosal colonization with *Staphylococcus aureus* and *Candida albicans* further complicate the scenario [19]. A summary of the immune responses negatively affected by diabetes and hyperglycemia is presented in Table 47.1.

Diabetes and Viral Infections

Viral infections are associated with metabolic derangements and predispose to the development of type 2 diabetes. The prevalence of type 2 diabetes in patients with hepatitis C is higher than in the general population. Hepatitis C promotes insulin resistance through multiple pathogenic mechanisms, including (1) defects in post-receptor insulin signaling, (2) high levels of proinflammatory cytokines, (3) high levels of reactive oxygen species, (4) low levels of GLP-1, (5) diminished glucose-stimulated insulin release, and (6) beta cell apoptosis [27]. Patients infected with the human immunodeficiency virus (HIV) are also at high risk of type 2 diabetes associated with the use of combination antiretroviral therapy. The HIV virus itself has been proposed as a mechanism of hyperglycemia, but the association between obesity and diabetes is strong, as in non-infected patients [28].

The Coronavirus Pandemic and Diabetes

> It appears now that a new group of viruses is emerging with members which infect the respiratory tract of birds and man.
> One member of the group, strain 229E, grows and produces cytopathic effect in tissue culture. (Kennett McIntosh et al. [29])

Coronaviruses are large, enveloped, single-stranded RNA viruses found in humans and other mammals such as dogs, cats, chicken, cattle, pigs, and birds [30]. Human coronaviruses have long been considered innocuous pathogens responsible for "the common cold" in healthy people [31]. In the twenty-first century however, two highly pathogenic coronaviruses emerged from animal reservoirs to cause global epidemics with high rates of morbidity and mortality: severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 in China and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 in Saudi Arabia [31, 32]. Clinically, flu-like symptoms are usual at the time of presentation for all three diseases, but these vary from asymptomatic to severe multisystem involvement [33]. The immune response to each of these viruses is highly complex and includes both humoral and cellular components that can have a significant impact on prognosis [33]. Global health studies confirmed higher mortality rates in persons with diabetes from infections caused by these viruses and announced the potential consequences of another emerging pandemic [24].

In December 31, 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood market selling many species of live animals in Wuhan China [31, 34]. This was reported to the World Health Organization Country Office, and the Chinese Centre for Disease Control and Prevention (China CDC) organized an intensive outbreak investigation program; by January 10, 2020, researchers from the Shanghai Public Health Clinical Center & School of Public Health released a full genomic sequence of 2019-nCoV to public databases [31, 34]. The etiology of the illness was attributed to a novel virus belonging to the coronavirus family, COVID-19, which is the acronym of "coronavirus disease 2019 [35]." COVID-19 is highly contagious and has quickly spread globally and primarily via respiratory droplets during close face-to-face contact. The average time from exposure to symptom onset is 4.6 days outside mainland China, 6.5 days in mainland China, and 5.1 days elsewhere [36, 37]. Starting with the first reports and afterwards, most of the infected patients are men and higher risk of infection is associated with comorbidities, such as diabetes, hypertension, obesity, respiratory and cardiovascular disease [32, 37, 38]. Of 120 studies with 125,446 patients, the most common comorbidities were hypertension (32%), obesity (25%), diabetes (18%), and cardiovascular disease (16%) [39]. Severity and risk of death from COVID-19 was associated with chronic kidney disease (51%), stroke (44%), and cardiovascular disease (44%) [40]. Systematic reviews and meta-analyses show that fatal outcomes associated with COVID-19 include male gender, older age, smoking, diabetes, obesity, chronic obstructive pulmonary disease, cardiovascular disease, cancer, acute kidney injury, and increased D-dimer [41]. The prevalence of comorbidities in people without diabetes is 25% [29] in comparison with 67% in people with diabetes [42], and the association with COVID-19 is more severe and conveys higher risks of mortality [42].

The World Health Organization classifies patients with COVID-19 into mild, moderate, severe, and critical disease [42]. Common symptoms include dry fever (77–90%), olfactory and/or gustatory dysfunction (64–80%), cough (64–86%), dyspnea (53–80%), myalgia (15–90%), or fatigue (38%); less common symptoms include sputum production, headache (16%), anorexia (19.4%), and diarrhea (9.42–39%) [30, 38, 43]. Clinical presentation of COVID-19 has several overlapping features with other pulmonary infections including pneumonia, chronic bronchitis, and chronic obstructive pulmonary disease [44, 45]. Mild disease is defined by patients meeting clinical and epidemiological criteria without the evidence of viral pneumonia or hypoxia, moderate disease is characterized by the evidence of pneumonia, severe disease is defined by pneumonia with a respiratory rate above 30 breaths/min or respiratory distress, and critical disease is defined by severe pneumonia complicated with respiratory distress syndrome, sepsis, or septic shock [45, 46].

Laboratory findings include a general decrease of the leukocyte count (21.5%), lymphopenia (50–83%), increased C-reactive protein level (58.3%), and high D-dimer levels (27–60%) [29, 46]. Liver function tests show increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) up to 18.3% and lactate dehydrogenase (48%) [30, 43]. Additional findings in chemical chemistry include increased high-sensitivity troponin (19%), creatinine kinase (42%), ferritin (14%), and serum creatinine (22.3%) [43]. Several biomarkers have become useful tools to differentiate patients with mild to severe COVID-19 infection including procalcitonin, C-reactive protein, serum amyloid A, interleukin-6, lymphocyte count, platelet count, lactate dehydrogenase, cardiac troponin, and serum ferritin [44]. Radiologic findings include patchy shadows in the peripheral zones of both lungs with higher involvement of the lower lobe of the left lung, ground glass opacities, and consolidations [43]. Laboratory tests for diagnosing COVID-19 infection include rapid antigen tests, serological testing, nucleic acid amplification tests, and viral sequencing [47]. Rapid antigen tests have the advantages of fast detection and low cost, but their disadvantages include (1) low sensitivity and specificity and (2) inability to identify patients in the incubation period [47]. Next generation sequencing is an accurate diagnostic method, but its high cost is an obstacle for widespread use [47]. Leading diagnostic tests for COVID-19 are IgM and IgG antibodies and nucleic acid amplification tests by real-time reverse transcriptase polymerase chain reaction (PCR) [47, 48]. Antibodies measure the immune response to COVID-19 infection and are detected in all patients between the third and fourth week of clinical illness [48]. IgM antibodies are detected 3–5 days after onset and IgG antibodies are above four times higher during the recovery period [47]. IgM titers begin to decline and reach lower levels after 5 weeks whereas IgG titers persist beyond 7 weeks [48]. The PCR test is highly sensitive and specific and has become the most commonly used and reliable test for diagnosis of COVID-19 [47].

The pathology associated with symptomatic severe acute respiratory syndrome and COVID-19 involves diffuse alveolar damage [33]. Complications include acute respiratory distress syndrome (ARDS) and multisystem involvement of the heart, brain, lung, liver, kidney, and coagulopathy [38, 45]. In severe cases, a dysregulated innate host immune system can initiate a hyperinflammatory syndrome dominated by endothelial dysfunction that may lead to a hypercoagulable state with microthrombi, resulting in microvascular and macrovascular diseases in children and adults [33, 49, 50].

Since the SARS COVID outbreak in 2002, extensive structural analysis revealed key atomic interactions between human pathogenic coronaviruses and host target cells through angiotensin-converting enzyme 2 (ACE2) receptor which is highly expressed by nasal and bronchial mucosal epithelial cells and pneumocytes [30, 51]. The high transmissibility of SARS-CoV-2 is probably related to active viral replication in the upper airways in the pre-symptomatic and symptomatic phases [52]. After receptor engagement, specific proteases like the type 2 transmembrane serine protease (TMPRSS2) present in alveolar epithelial type II cells, cleave the S protein, and trigger its fusion to cells (fusogenic activity) [30, 52]. Binding of ACE2 to the viral structural spike S protein induces endocytosis of the virion, fusion of the viral envelope with the endosomal membrane to enable the release of the viral genome into the cytoplasm or alternatively at the plasma membrane after receptor engagement [52]. Severe lymphopenia occurs and the host response to the virus activates the innate and adaptive immune system, additionally impairing lymphopoiesis and increasing lymphocyte apoptosis [30]. Observational studies have demonstrated strong antibody and T cell responses in a large proportion of patients, but the humoral response appears to be proportional to COVID-19 severity [45]. In later stages of the infection, epithelial-endothelial barrier integrity is compromised; COVID-19 infects pulmonary capillary endothelial cells, increasing the inflammatory response and the influx of monocytes and neutrophils. The last stage in severe COVID-19 involves critical activation of coagulation and consumption of clotting factors, viral sepsis, organ dysfunction, and multiorgan failure [30]. Extrapulmonary manifestations of COVID-19 involve brain/nervous system, kidney, liver, gastrointestinal tract, heart/cardiovascular system, endocrine system and skin with corresponding myriad symptoms and signs [45].

According to early data reported by CDC China from more than 44,000 confirmed cases of COVID-19 infection, death rates among patients with diabetes were 7.0% compared with 0.9% in people without diabetes [34]. Impaired immune function is a clinical feature of COVID-19 infection. As already mentioned, diabetes is characterized by defects in innate and adaptive immune responses in addition to micro-angiopathic changes in the respiratory tract and other organ systems, contributing to the progression and poor prognosis of COVID-19 (Table 47.2) [24, 30, 53].

Table 47.2 Immune abnormalities against COVID-19 in diabetes

Immune response	Cell type	Abnormality
Innate	Macrophages	Lung accumulation, ↑ proinflammatory activity
	Dendritic cells	↓ Amount and function
	Neutrophils	Entrapment, ↑ ACE2 receptors
	NK cells	↓ Function
	NKT cells	↑ CD57 and CD
Adaptive immunity	B cells	Changes in number, phenotype, and function
	T cells	Targeting of CD4T cells against viral spike protein

Modified from references [24, 30, 51]

Pathophysiology of COVID-19 Infection in Hyperglycemia and Diabetes

Hyperglycemia and diabetes are long-established risk factors for viral infections and pneumonia [54]. Diabetes induces lung oxidative stress and inflammation, apoptosis of alveolar cells, persistent matrix deposition, and increases the susceptibility to viral pneumonia [55]. In addition, diabetes induces functional abnormalities in the lung, including decrease in volumes, elastic recoil and diffusion capacity, and oxidative stress injury to pancreatic beta cells [55, 56]. Compared with hospitalized patients with COVID-19 without diabetes, patients with diabetes have worse clinical profiles and outcomes including higher levels of glucose, HbA1c, leukocytes, high-sensitive C-reactive protein, procalcitonin, ferritin, D-dimer, lactic dehydrogenase, natriuretic peptide, severity of disease, higher frequency of admission to intensive care units, and mortality [55, 56]. Plasma glucose levels and diabetes are independent predictors of mortality and morbidity in patients with COVID-19 infection, and mechanisms that increase the vulnerability include increased binding affinity and efficient virus entry, reduced viral clearance, impaired T cell function, increased susceptibility to cytokine storm, cardiovascular and pulmonary preexisting disease [55]. Host-cellular protein components involved in the entry of COVID-19 [55] include angiotensin-converting enzyme-2 (ACE2), Furin, serine protease TMPRSS2, interferon-induced transmembrane proteins (IFITM), desintegrin, and metalloproteinase domain 17 proteins (ADAM17) [55]. Patients with type 2 diabetes present more severe inflammatory responses and less lymphocyte counts than patients without diabetes, are more likely to worsen from moderate to severe disease, and inflammation and lymphocyte recovery are slower [57]. Respiratory viral infections predispose to bacterial co-infections leading to increased disease severity and mortality, particularly in people with diabetes [58].

Management of Patients with COVID-19 and Diabetes

Patients with diabetes require more medical interventions and had significantly higher mortality and multiple organ injury than patients without diabetes [59]. Glucose control is associated with markedly lower mortality compared to patients with poor glycemic control (above 180 mg/dL) and is a leading goal of treatment [59]. Management of patients with diabetes and infection by COVID-19 involves general and metabolically oriented measures, summarized in Table 47.3 [46, 60–69].

Table 47.3 General management of COVID-19 infection in people with diabetes [60–72]

HbA1c: <7.0%		
Fasting plasma glucose: 72.0–144 mg/dL		
Avoid hypoglycemia: <55.0 mg/dL		
Blood pressure: <140/80 mm Hg		
Low-density lipoproteins: <100 mg/dL		
Assessment and control of comorbidities		
Stage	**Recommendation**	**Comments**
	Sensitization about the importance of optimal metabolic control	
Primary prevention	Reduce social contact	Key measure to contain the spread
	Strategies of virtual support, including telephone and telemedicine	
	Vaccination	**BNT162b2 mRNA, two dose regimen**
		Efficacy: 89.0% in preventing hospitalization from COVID-19; 90.0% in preventing admission to intensive care unit; 91.0% in preventing emergency department or urgent care visit; ranging from 81.0% to 95.0% across subgroups defined by age, sex, race, ethnicity, body mass index, and comorbidities
		Safety profile: short-term, mild to moderate pain at the injection site, fatigue, and headache
		Low incidence of serious adverse effects, similar rates in the vaccine and placebo groups
		Antibody titers decline sharply by 6 months after vaccination and decline further after 8 months
		mRNA-1273 SARS-CoV-2, two dose regimen
		Efficacy: 94.1% across key secondary analyses, including 14 days after the first dose, evidence of SARS-CoV-2 infection at baseline and in people ≥65 years old
		Safety: moderate, transient reactogenicity, serious adverse events are rare and similar in patients receiving the vaccine or placebo
		Binding and functional antibodies against variants persist in most vaccinated subjects albeit at low levels, 6 months after the first dose
		Neutralizing antibody titers significantly decreased after 8 months
		Ad26.COV2.S, one dose versus two-dose regimen
		Efficacy: 76–83% in adults 18–55 years old; 60–77% in patients ≥65 years and older; 68.0% in preventing hospitalization, 73.0% in preventing emergency department or urgent care clinic visit
		Safety: most frequent adverse events included fatigue, headache, myalgia, pain in the site of injection, and fever, especially in patients ≥65 years old
		Differential kinetics of immune responses: substantially lower median titers than mRNA vaccines at peak immunity, 4 weeks after first dose, albeit remained stable over 8 months
		Purified inactivated SARS-Cov-2, two-dose regimen
		Efficacy: 65.6% for prevention, 87.0% for preventing hospitalization, 90.3% for preventing admission to intensive care unit, 86.3% for preventing COVID-19 death
		AZD1222 (ChAdOx1 nCoV-19), two-dose regimen
		Efficacy: 74.5% overall, 83.5% in people ≥65 years old; efficacy for preventing COVID-19 infection: 64.3%
		No severe or critical symptomatic COVID-19 cases among people vaccinated
		Spike binding and neutralizing antibodies increased after the first dose and increased further when measured 28 days after the second dose
		Safety: low incidence of serious and medically attended adverse events and similar frequency with placebo; mild or moderate local and systemic reactions in both groups
		Overall waning vaccine immunity, correlates of protection not yet defined
	Wearing masks	Control the source of infection
	Hand hygiene	Protect susceptible groups
		Reduce the risk of health providers from being infected when attending to patients
		Significant inhibitory effect on the spread of respiratory viruses for healthcare providers (80%) and non-healthcare workers (47%)
	Antidiabetics	All therapeutic classes
Mild COVID-19	Isolation to contain viral transmission	On an individual basis
		Close monitoring
	Symptomatic treatment	Analgesics
		Antipyretics

Table 47.3 (continued)

	Adequate nutrition and hydration	
	Patient and family counseling	Advise about signs and symptoms of disease complications and progression including dyspnea, chest pain, and dehydration
	Antidiabetics	At usual doses:
		Metformin
		Anti-inflammatory, antithrombotic properties, reduce mortality in type 2 diabetes patients with COVID-19
		Prevention of cytokine storm
		DPP-4 inhibitors
		Prevention of coronavirus from entering host cells
		Anti-inflammatory effects
		SGLT-2 inhibitors
		Increase the expression of ACE2 in the kidney, increase susceptibility to infection
		GLP-1 receptor agonists
		Systemic anti-inflammatory properties
		Insulin
		Downregulation of ACE2 receptors
		Anti-inflammatory, antithrombotic effect
		Sulfonylureas
		A-glucosidase inhibitors
		Use with caution:
		Thiazolidinediones
		Weight gain, fluid retention, edema, increasing heart failure
Moderate COVID-19	Immediate isolation to contain viral transmission on an individual basis, depending on clinical presentation, requirements for supportive care, risk factors for severe disease and conditions at home	At health facility
		At community facility
		Self-isolation at home
	Regular monitoring	Pulse oximetry
		Temperature
		Blood pressure
	Testing and treatment for other infections causing fever	Routine use of antibiotics not advised
	Antidiabetics	At usual doses:
		DPP-4 inhibitors
		SGLT-2 inhibitors
		GLP-2 receptor agonists
		Insulin
		Use with caution
		Metformin
		A-glucosidase inhibitors
		SGLT-2 inhibitors
		Contraindicated
		Thiazolidinediones
		Sulfonylureas
Severe COVID-19	Supplemental oxygen in patients with oxygen saturation levels <90.0%	Emergency airway management, target oxygen level ≥94.0%
		Nasal cannula for flow rates up to 5 L/min
		Venturi mask for 6–10 L/min
		Face mask with reservoir bag for 10–15 L/min
	Continuous monitoring for signs of clinical deterioration	Hematological and biochemical laboratory testing
		Electrocardiogram
		Chest imaging
	Immediate supportive care	Intravenous fluids
	Antidiabetics	At usual doses:
		DPP-4 inhibitors
		Insulin
		Contraindicated:
		Metformin
		α-glucosidase inhibitors
		SGLT-2 inhibitors
		Thiazolidinediones

(continued)

Table 47.3 (continued)

Critical COVID-19	Supplemental oxygen in patients with oxygen saturation levels <90.0%	Emergency airway management, target oxygen level ≥94.0%
		Mild acute respiratory distress syndrome:
		Noninvasive ventilation through continuous positive airway pressure and bilevel positive airway pressure
		Invasive ventilation including endotracheal intubation and tracheostomy in patients with hypercapnia, hypoxemic respiratory failure, hemodynamic instability, multiorgan failure, or abnormal mental status
		Prone ventilation 12–16 h/day
	Continuous monitoring for signs of clinical deterioration	Hematological and biochemical laboratory testing
		Electrocardiogram
		Chest imaging
	Immediate supportive care	Intravenous fluids
	Antivirals	Remdesivir: 200 mg/IV on day 1, 100 mg/IV on days 2–10
	Antidiabetics	At usual doses:
		DPP-4 inhibitors
		Insulin
		Contraindicated:
		Metformin
		α-glucosidase inhibitors
		SGLT-2 inhibitors
		Thiazolidinediones
Post-COVID	Monitoring for metabolic, physical, psychosocial, and cognitive impairments	Glycemic control
		Blood pressure control
		Lipoprotein profile control
		Rehabilitation
		Vaccination prioritization

As already mentioned, diabetes is a relevant comorbidity in people with COVID-19 infection and increases the risk of severity and mortality. Glycemic and overall metabolic control are essential at every stage. Patient and family support to address the disease and its consequences in mental health is also important.

By the end of October 2021, the WHO estimated more than 243 million confirmed cases of COVID-19 globally, 4.9 million deaths, and a mortality rate of 2.03% [73]. Since the beginning of the pandemic, diabetes was identified as an important risk factor for mortality and progression to acute respiratory distress syndrome in patients with COVID-19 [74]. After 18 months, epidemiologic studies confirm that diabetes is a central contributor to severe COVID-19 morbidity and that COVID-19 has had devastating effects on people with diabetes [75]. The evidence is compelling. Patients with type 1 or type 2 diabetes (1) represent 30–40% of hospital admissions by COVID-19, (2) 21–43% of people requiring intensive care, and (3) have a mortality rate of 25% [75]. The risk of severe morbidity and mortality is 100–250% higher among people with diabetes and the impact on the general population with diabetes has been 50% higher than historical trends, more than twice that of the general population [75].

The emergence of the COVID-19 pandemic has become a landmark in the history of mankind, a mass casualty incident [76]. Its effects at the global, political, economic, and individual level have been devastating and at the end of 2021 continue to be evolving. Quantifying the overall impact and its morbidity and mortality is still not feasible until cascades of metrics including (1) population at risk, (2) population exposed, (3) people infected, (4) people diagnosed, (5) people hospitalized, (6) people with severe forms of disease, and (7) mortality can be constructed at the global, regional, and national level. Living with diabetes during the COVID-19 pandemic is challenging. The established complexities of diabetes management have been exacerbated by the scarcity of access to healthy foods, scarcity of medicines or access to medical services, and limited physical activity or exercise because of confinement [77].

Diabetes Parasitic Diseases and "The Hygiene Hypothesis"

In comparison with the high risk of bacterial, fungal, and viral infections, an inverse association between soil-transmitted helminthiasis and diabetes was initially reported by Nazligul and colleagues in 2001 [78]. The evidence is scarce and comprises six experimental studies and seven cross-sectional studies which were summarized by de Ruiter and colleagues [79]. Under the hypothesis that having diabetes would affect the susceptibility to infections, six of these studies showed that the prevalence of intestinal parasites was significantly lower among patients with diabetes; by comparison, only one small study in Brazil reported a positive association between *Strongyloides stercoralis* infection and type 2 diabetes [80]. In this study, the frequency of positive *S. stercoralis* serology in diabetics was 23% versus 7.1% in the control group ($p < 0.05$).

The odds ratio for diabetics was 3.9 (CI, 1.6–15.9, $p < 0.05$) [80]. By comparison, the remaining six studies showed a significantly lower prevalence of intestinal helminth infections in patients with type 2 diabetes, metabolic syndrome, or insulin resistance [79]. The inverse relation or "protective effect" of type 2 diabetes and helminth infections could be related to a state of cellular immune hypo-responsiveness induced by parasites mediated by a helminth-induced regulatory network involving regulatory T cells and their associated cytokines IL-10 and transforming growth factor-β [81]. These observations are related to the revised hygiene hypothesis proposed by Strachan in 1989, who proposed that improved hygiene increased the rise of allergic diseases [81]. This hypothesis states that exposure to pathogens is critical to establish immunomodulatory cells to prevent inappropriate responses [81]. Albeit strongly criticized as "a dangerous misnomer which is misleading people away from finding the true causes of the rise in allergic disease [82]" and should not diminish the importance of personal hygiene in every age group, the inverse association between helminth infections and type 2 diabetes is an interesting observation that invites further study.

Categories of Infections in Patients with Diabetes

Three categories of infections have been described: (1) common infections also occurring in persons with diabetes; (2) uncommon infections strongly associated or typical of diabetes; (3) infections related to therapeutic interventions in people with diabetes [2]. The spectrum of disease and the likely causative organisms identified in people with diabetes are presented in Table 47.4.

Table 47.4 Disease spectrum, causative microorganisms, and main clinical features

	Spectrum of infections and references	Causative microorganisms	Clinical features	Diagnostic procedure
Head and neck				
	Herpes zoster ophthalmicus [83–86]	Human herpes virus type 3	Risk ratio: 1.31 (95% CI, 1.22–1.41)	Complete medical history Ophthalmologic examination
			Represents 10–20% of herpes zoster cases, 3.2 cases per 1000 person-years	
			Peak incidence: 50–79 years, higher in patients over 80 years	
			Three clinical phases: (1) Pre-eruptive, (2) acute eruptive, (3) chronic.	
			(1) Pre-eruptive symptoms and signs: headache, fatigue, malaise, photophobia, and fever; neuralgia around the eye and forehead with pinprick anesthesia and hyperesthesia to light touch (allodynia)	
			(2) Acute eruptive phase: involves skin, eyelids, the medial canthal area, conjunctiva and cornea. Skin lesions manifest as a vesicular eruption along the ophthalmic dermatome of the trigeminal nerve, erythematous coalescing papules evolving into clear vesicles with rupture, secondary bacterial infection, and discharge, and crusting over several weeks. The Hutchinson sign refers to involvement of the tip of the nose. Eyelid involvement includes cutaneous macular rash, ptosis, and lagophthalmos. Signs of conjunctival involvement include injection and chemosis with papillary reaction, hyperemic mucopurulent conjunctivitis, and petechial hemorrhages.	
			(3) Chronic stage: cornea and anterior segment: punctuate epithelial keratitis and pseudodendrites, nummular stromal keratitis, disciform stromal keratitis, neurotrophic keratopathy corneal neovascularization, lipid extravasation, and opacification diminished corneal sensation, corneal ulceration, eye perforation, uveitis, secondary glaucoma	
			Posterior segment: acute optic neuritis, orbital phlegmon, superior orbital fissure syndrome necrotizing retinopathy, and blindness.	
			Cranial nerves: Additional compromise includes involvement of the iris, the retina, and the optic nerve, motor palsies of the third, fourth, and sixth, diplopia.	
			Late complications: postherpetic neuralgia in 20% of the patients, higher in the elderly or in patients with involvement beyond the skin	

(continued)

Table 47.4 (continued)

	Spectrum of infections and references	Causative microorganisms	Clinical features	Diagnostic procedure
	Malignant external otitis [2, 87–89]	*Pseudomonas aeruginosa*	Three clinical stages: (1) Infection of the external auditory canal and adjacent soft tissues	Clinical examination
		Methicillin resistant *Staphylococcus aureus*	(2) Extension of infection with osteitis of skull base and temporal bone	Ear swab culture Positive Technetium (^{99}TC) scan of failure of local treatment after more than 1 week
		Proteus mirabilis	(3) Dissemination to intracranial structures, neck spaces, and large blood vessels	Computed tomography, magnetic resonance imaging to assess progression and resolution
		Klebsiella oxytoca	Major obligatory signs: Unrelenting pain	Culture of drainage material
		Pseudomonas cepacia	Otorrhea Edema	Biopsy from the infection site
		Staphylococcus epidermidis Candida *Aspergillus fumigatus*	Granulations	Histological examination shows nonspecific inflammation and hyperplasia of squamous epithelium
		Polymicrobial infections	Microabscesses	
			Minor or occasional: Hearing loss	
			Pain at the temporomandibular joint	
			Cellulitis	
			Osteomyelitis of the skull base	
			Cranial nerve palsies: Common: facial, glossopharyngeal, vagal, spinal accessory	
			Less common: hypoglossal Rare: trigeminal, abducens, optic	
	Periodontal infections [90, 91]	Most associated pathogens are indigenous to the oral cavity, but possible superinfecting microorganism may also inhabit periodontal pockets	Pain, gingival swelling	Oral examination
		Lesions usually contain a constellation of pathogens, mostly gram-negative anaerobic, but also gram-negative facultative rods		
	Oral candidiasis [92]	*Candida albicans*, Pichia, Trichosporon, Geotrichum	May be asymptomatic	Dental examination
			Sore throat, dysphagia	
			White patches on the surface of the oral cavity	
			Untreated candidiasis may lead to chronic hyperplastic candidiasis: candidal leukoplakia	
	Rhino-orbital or rhino-cerebral sinusitis [92–95]	Rhizopus, mucor, and absidia species	Preseptal or orbital cellulitis: Facial or ocular pain, fever, headache, nasal discharge, sinus pain	Clinical examination, culturing, magnetic resonance, histopathological evidence of fungal invasion of tissue
			Facial erythema or cyanosis	
			Sub-periosteal or orbital abscess: perinasal swelling, edema, proptosis, chemosis and even blindness	
			Facial numbness from damage to sensory branches of the fifth cranial nerve	
			Black, necrotic eschar on the palate or nasal mucosa, turbinate destruction	
			Intracranial complications: epidural and subdural abscesses, necrosis of frontal lobes, cavernous and sagittal sinus thrombosis	
			Clinical meningitis is rare	

Table 47.4 (continued)

	Spectrum of infections and references	Causative microorganisms	Clinical features	Diagnostic procedure
Respiratory system	Influenza [96, 97]	Type A influenza viruses: H1N1 and H3N2	Six times more frequent in patients with diabetes	Normal or decreased leukocyte count
			Wide range of manifestations, including: (1) asymptomatic, (2) conjunctivitis, (3) influenza-like illness, (4) viral pneumonia, (5) acute respiratory distress syndrome, (6) respiratory failure, (7) multiorgan failure	Lymphopenia and thrombocytopenia, high levels of C-reactive protein
			Sudden onset: fever, cough, malaise, wheezing, pulmonary rales, respiratory failure	Chest radiography: ground glass opacities and consolidation
				Confirmatory tests for influenza H1N1 including real-time or reverse transcriptase polymerase chain reaction
	Community-acquired pneumonia [98–110]	Outpatient: *Streptococcus pneumoniae*	Cough, fever, dyspnea, focal chest signs, respiratory failure	Clinical examination
		Mycoplasma pneumoniae	Prediction rule for diagnosis: Rhinorrhea—2, Sore throat—1, Night sweats 1, Myalgia 1, Sputum 1, Respiratory rate >25 breaths/min	Chest radiography
		Chlamydia pneumoniae	2 Temperature ≥100 °F (37.8 °C)	Pathogens are not detected in half of pneumonia episodes
		Klebsiella pneumoniae	2 Positive likelihood ratio: 3 points 14.0, 1 point: 5.0, −1 point: 1.5, ≤10.2 points	Clinical indications for extensive diagnostic testing include: (1) intensive care unit admission, (2) failure of outpatient antibiotic therapy, (3) cavitary infiltrates, (4) leucopenia, (5) alcoholism, (6) chronic liver disease, (7) obstructive/structural lung disease, (8) recent travel, (9) positive Legionella urinary antigen result, (10) positive urinary antigen pneumococcal result, (11) pleural effusion
		Legionella pneumophila		
		Haemophilus influenzae		
		Respiratory viruses		
		Inpatient, non-intensive care unit		
		Streptococcus pneumoniae		
		Mycoplasma pneumoniae		
		Chlamydia pneumoniae		
		Haemophilus influenzae		
		Legionella sp. aspiration		
		Intensive care unit		
		Streptococcus pneumoniae		
		Staphylococcus aureus		
		Legionella pneumophila		
		Gram-negative bacilli		
		Haemophilus influenzae		
	Pulmonary tuberculosis [111–114]	*Mycobacterium tuberculosis*	Fever, night sweats, weight loss, cough, sputum, hemoptysis	Chest radiography usually shows more lung cavities and parenchymal lesions in patients with diabetes than patients without diabetes. Sputum microscopy and culture: bacilloscopy from two samples collected at the same visit
			Patients with tuberculosis and diabetes are reported to be older and heavier, and more likely to be male	Xpert MTB/RIF: *M. tuberculosis* PCR

(continued)

Table 47.4 (continued)

	Spectrum of infections and references	Causative microorganisms	Clinical features	Diagnostic procedure
	Pulmonary coccidioidomycosis [115]	*Coccidioides immitis*, *Coccidioides posadasii*	Asymptomatic or mild respiratory illness in most cases	Chest radiography showing segmental or lobar consolidations, hilar or mediastinal adenopathy, pleural effusions, residual nodules, cavities, and chronic infiltrates
			Patients with diabetes may present with diffuse pneumonia	Definitive diagnosis is serological, by means of immunodiffusion to detect immunoglobulin G and IgM-specific antibodies
			Symptoms of severe illness include fever, malaise, pneumonia, chronic structural lung disease or cardiopulmonary disease, respiratory distress syndrome	Complement fixation tests for IgG-specific antibodies are useful in immunocompetent patients
			Improvement is slow in these cases	
	Pulmonary mucormycosis [92–95]	Rhizopus, Mucor	Pneumonia refractory to antibacterials	Computed tomography
			Hemoptysis	Histopathology
			Multiple mycotic pulmonary artery aneurisms and pseudoaneurysms, bronchial obstruction, asymptomatic solitary nodules	
			Endobronchial lesions with resulting obstruction of major airways or erosion into pulmonary blood vessels	
			Less common complications include mycetomas in preexisting lung cavities or slowly necrotizing pneumonia, hypersensitivity syndromes, and allergic alveolitis	
Abdomen	Acute emphysematous cholecystitis [1, 116, 117]	*Clostridium perfringens*	Fever, right upper quadrant abdominal pain, vomiting, jaundice, peritonitis, septic shock, sepsis	Radiography
		Escherichia coli		Computed tomography
		Bacteroides fragilis		
	Pyogenic liver abscess [118–120]	Invasive *Klebsiella pneumonia* serotypes K1 and K2	Fever, chills, and abdominal pain; nausea and vomiting	Computed tomography
			Higher rates of cryptogenic etiology, gas-forming nature, thrombocytopenia, growth of *Klebsiella pneumoniae* in blood cultures, metastatic infection, and bacteremia in patients with diabetes	Isolation of *Klebsiella pneumoniae* from blood or liver abscess
			Lower rates of right upper quadrant pain, biliary origin	Multiplex PCR
	Psoas and spinal epidural abscess [121, 122]	Most frequent: *Staphylococcus aureus*, but also *Escherichia coli*, *Mycobacterium tuberculosis*, Enterobacter, and Klebsiella	May be primary, from hematogenous spread from an occult source, or secondary, by spreading from contiguous anatomical structures	Leukocytosis
			Back pain, in the flank in the buttock or in the leg, fever, malaise	Computed tomography
Genitourinary tract	Asymptomatic bacteriuria [123, 124]	*Escherichia coli*	Asymptomatic	Urine examination and culture
		Staphylococcus saprophyticus		
		Enterococcus sp.		
		Candida		
	Candiduria [125]	*Candida* sp.	Frequently asymptomatic	Clinical examination
			Rare complications include prostatitis and epididymo-orchitis	Urinary dipstick, microscopy, urinary culture
	Acute pyelonephritis [126–129]	Bacterial: *Escherichia coli* Fungal: *Candida* sp.	Presentation of symptoms is variable, ranging from fever, malaise, costovertebral angle pain and tenderness, urgency and dysuria, to intense pain, nausea, vomiting, sepsis and septic shock in severe cases	Clinical examination
				Urinary dipstick, microscopy
				A quantitative count of $\geq 10^3$ cfu/mL in the urinary culture
				Pyuria

Table 47.4 (continued)

	Spectrum of infections and references	Causative microorganisms	Clinical features	Diagnostic procedure
	Emphysematous pyelonephritis [129]	*Escherichia coli*	Fever, chills, abdominal and flank pain, nausea, vomiting, dysuria, pyuria	Renal ultrasound, computed tomography
		Klebsiella pneumonia	Associated with poor prognosis: thrombocytopenia, mental status changes, proteinuria	
		Proteus mirabilis		
		Pseudomonas aeruginosa		
		Citrobacter		
		Candida		
	Perinephric abscess [130]	Common: *Escherichia coli*, *Enterobacter* sp., *Pseudomonas aeruginosa*, *Serratia* sp., *Citrobacter* spp.	Chronic presentation: persisting urinary infection, urine culture positive for *Proteus* spp.	Renal ultrasound, computed tomography, magnetic resonance imaging
		Less frequent: *Clostridium* spp. Bacteroides, *Actinomyces* spp., *Corynebacterium urealyticum*	Flank tenderness, localized rigidity and fullness, scoliosis, and palpable mass in some cases	
		Tuberculosis should always be considered	Signs in advanced stages: anemia, malaise empyema, psoas abscess or pyonephrosis necessitans	
		Proteus mirabilis in infected calculi	Acute: chills interspersed with high fever, loin and flank tenderness, history of bacterial skin infection	
	Bacterial cystitis [123, 124, 127, 128]	*Escherichia coli*	May be asymptomatic	Medical history
			More frequent in patients treated with sodium-glucose cotransporter-2 inhibitors	Urinalysis, urine culture
			Urgency, dysuria, fever	
	Fungal cystitis [125]	*Candida albicans*	Severe urgency, frequency, and nicturia	Medical history
			Sterile pyuria, microhematuria	Urine examination and culture
	Emphysematous cystitis [129]	More frequent: *Escherichia coli*, *Klebsiella pneumoniae Enterobacter aerogenes*, *Proteus mirabilis*, *Streptococcus* sp.	From asymptomatic (7%) to severe sepsis	Clinical examination: history of neurogenic bladder, complicated urinary tract infections, bladder outlet obstruction
		Less common: *Pseudomonas aeruginosa*, *Candida albicans*, *Clostridium perfringens*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Clostridium welchii*, *Candida tropicalis*, *Aspergillus fumigatus*	Common symptoms: abdominal pain (80%) and gross hematuria (60%)	Urine examination and culture
			Less common: fever (30–50%), pneumaturia, dysuria, urinary frequency and urgency (50%)	Blood culture
				Plain film of the abdomen showing curvilinear areas of increased radiolucency delineating the bladder wall and intraluminal gas
				Computed tomography
	Vulvovaginal candidiasis [92, 131–136]	*Candida albicans*, *Candida glabrata*, *Candida tropicalis*	May be asymptomatic	Medical history
			Risk in patients treated with sodium-glucose cotransporter-2 inhibitors: 3–5 higher	Clinical examination of vaginal secretions including culture and wet mount, KOH microscopy, gram stain, Whiff test, pH measurement
			Acute pruritus, vaginal discharge, vaginal soreness, irritation, vulvar burning, dyspareunia, dysuria, odor, erythema, swelling of the labia and vulva	

(continued)

Table 47.4 (continued)

	Spectrum of infections and references	Causative microorganisms	Clinical features	Diagnostic procedure
	Balanoposthitis [137]	*Candida glabrata*, *Candida albicans*, *Candida tropicalis*	More frequent in uncircumcised men and in patients treated with sodium-glucose cotransporter-2 inhibitors	Medical history Physical examination
		Streptococci, Staphylococci, anaerobic bacteria, *Trichomonas vaginalis*, *Mycoplasma genitalis*, and herpes simplex virus have also been associated	Balanitis involves inflammation of the glans penis; posthitis is defined as inflammation of the prepuce	
	Necrotizing fasciitis [1, 2, 13]	*S. pyogenes*, *Clostridium* sp.	Pain, erythema, crepitation, bullous skin lesions	Medical history
			Involvement of skin, subcutaneous tissue, and superficial fascia	Clinical examination
				Plain radiography, computed tomography, or magnetic resonance imaging of the affected area
				Biopsy, gram stain, and culture
	Fournier's gangrene [138]	Mixed aerobes and anaerobes including *Escherichia coli*, *Klebsiella pneumoniae*, *Bacteroides fragilis*, Streptococcus, Enterococcus, Clostridium, Pseudomonas and Proteus	Male/female ratio: 10 to 1	Clinical examination
		Uncommon: Candida, *Lactobacillus gasseri*	Sudden pain and swelling in the scrotum	Imaging rarely necessary to ascertain extension
			Purulence or wound discharge, crepitation, fluctuance, prostration, fever	
			Necrotizing fasciitis of the external genitalia	
			Localized tenderness and wounds in genitalia and perineum	
			Fetid drainage and sloughing in affected sites	
			Sepsis, multiorgan failure	
Upper and lower extremities, skin and appendages	Hand ulceration and infection, "tropical diabetic hand syndrome" [139, 140]	*Staphylococcus* sp.	Under-reported, very few physicians are aware of its existence, resulting in late diagnosis and proper treatment	Clinical examination
			Largely reported in African countries, but also in the United States	Wound swab and culture
			More frequent in patients living in tropical and coastal areas	
			History of trauma including mild abrasions, lacerations, and insect bites; poor glycemic control, delayed presentation	
			Clinical presentation variable, ranging from localized swelling, cellulitis, and exudate, with or without ulceration, progressive hand sepsis and gangrene	
	Cutaneous zygomycosis [93, 94]	*Rhizopus* sp.	Single, painful area of erythema, induration, and cellulitis	Clinical examination
			Portals of entry include contaminated wounds, traumatic wounds, dressings, burns, and surgical sites	Skin biopsy
			Lesions secondary to trauma rapidly develop necrosis and extension to subcutaneous tissues, similar to ecthyma	
	Cellulitis [2, 6, 20, 141, 142]	*Staphylococcus aureus*, *Streptococcus pyogenes*, gram negatives and anaerobes less common	Painful, erythematous infection of the dermis and subcutaneous tissues presenting with warmth, edema, and advancing borders	Biopsy and histology examination
			Fever and leukocytosis	
			Most common sites include legs and digits, the face, feet, hands, torso, neck, and buttocks	

Table 47.4 (continued)

	Spectrum of infections and references	Causative microorganisms	Clinical features	Diagnostic procedure
	Foot ulcer infections [142–145]	Usually polymicrobial, including *Staphylococcus aureus*, *Proteus* spp., *Escherichia coli*, *Peptostreptococcus* sp., *Veilonella* sp., *Bacteroides* sp., *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*	Contaminating ulcers in the plantar aspect of foot, tip of the toe, lateral to fifth metatarsal	Culture preferably from tissue specimens rather than swabs
			Presence of purulence or at least ≥2 classic symptoms or signs of inflammation: erythema, edema, warmth, tenderness, pain, or induration	Deep tissue sampling; curettage or tissue scraping from the base of the ulcer
			In case of neuropathy, secondary signs include discolored granulation tissue, foul odor, non-purulent discharges, delayed wound healing	Gram staining and microscopy examination
	Herpes zoster [146, 147]	Varicella zoster virus	Odds ratio in patients with diabetes: 1.20 (CI 1.17–1.22)	Clinical examination
			Localized pain and paresthesia followed by erythematous macules or papules coalescing into grouped vesicular lesions or bullae usually in one dermatomal distribution, and unilateral	PCR testing for viral DNA from fluid from skin lesions
			Pustules and crusting afterwards	Direct fluorescent antibody testing on scrapings from active lesions
			Complete healing up to 4 weeks	
			Most common sites are the thoracic nerves and the ophthalmic division of the trigeminal nerve	
			Systemic symptoms include fever, headache, malaise, and fatigue	
	Tinea pedis, intertrigo [92]	*Candida*	Itching and scaling of the affected skin	Clinical examination
			Plantar or intertriginal fissures	Fungal culturing of skin samples
			Paronychial inflammation of the edge surrounding skin	
	Onychomycosis [92, 148, 149]	Dermatophytes: *Trichophyton rubrum*, *Trichophyton mentagrophytes*	Dystrophic, thick, brittle, and discolored nails, distal onycholysis, subungual hyperkeratosis, thickening of the nail bed and nail plate	Fungal culturing of samples from nail plates or subungual debris, direct microscopy
		Non-dermatophytes: *Candida* sp.		Histopathological examination
Hospital-acquired infections [2, 6, 20, 92, 124]				
Local	Postoperative wound infections	*Staphylococcus aureus*	7.7 higher risk	Clinical examination
			Mortality related to time with diabetes, glycemic control at hospital admission, and A1c level	Swab or biopsy examination
			Postoperative infections have been described in multiple surgical settings, including cardiothoracic, general, orthopedic, and vascular	
Systemic	Fungemia	*Candida albicans, Aspergillus fumigates, Candida glabrata*	Associated with disruption of skin barriers including injections or intravascular access	Clinical suspicion, isolation, and identification of pathogens by culturing and histopathology
	Mycosis in hemodialysis patients	*Candida* spp.	High risk in patients with onychomycosis	Clinical suspicion, isolation, and identification of pathogens by culturing and histopathology
	Urinary tract infection in post-renal transplant patients	*Escherichia coli*	Prevalence: 25–47%, higher risk in the first year post-transplant	Clinical examination, urine examination, and culture
			Additional risk factors include indwelling devices, immunosuppressive therapy and urologic abnormalities	
			May be asymptomatic or present with graft tenderness	
	Mycosis in post-transplant patients, including kidney and pancreas	*Candida* spp. *Cryptococcus neoformans*	May be asymptomatic	Clinical examination
				Blood culture

(continued)

Principles of Management

Managing infections in persons with diabetes is always a challenge for physicians. Principles of management include the following.

Awareness of Diabetes-Associated Diseases

Awareness regarding the variety and severity of diseases, in persons with diabetes, is essential for prevention and prompt treatment. Diabetes education, along with optimal glycemic control, can minimize the risk of life-threatening infections. Simple preventive measures like proper foot care can reduce disease-associated morbidity.

Adequate Choice of Antibiotics

Empirical broad-spectrum antibiotics should be used till microbiologic results can guide treatment; some infections are frequently resolved empirically. Choice of antibiotics should be based on possible causative organisms and local flora. Early suspicion of antibiotic resistance, in people with diabetes with complicated infections, can help in limiting the disease-associated morbidity and mortality. *P. aeruginosa* infections are commonly seen in hospitalized patients with cystic fibrosis, cytotoxic chemotherapy, mechanical ventilation, and broad-spectrum antibiotic therapy. Patients present with fever, shock, hypothermia, acute pneumonia, and occasionally ecthyma gangrenosum. Table 47.5 shows empirical therapies for infections in patients with diabetes, and Table 47.6 presents first

Table 47.5 Empirical selection of antimicrobial therapy and dose in adults

Infection	First choice	Alternate choice(s)
Herpes zoster ophthalmicus	Acyclovir, 800 mg PO five times daily/7–10 days	Valacyclovir 1000 mg PO three times daily/7–10 days
		Famciclovir, 500 mg PO/three times a day/7–10 days
Malignant external otitis (MEO)	Ciprofloxacin, 1.5 g IV/day plus Ceftazidime 2 g IV/8 h/10 weeks	Itraconazole, 200 mg PO or Voriconazole 200 mg PO daily/6 weeks, for MEO caused by Aspergillosis
Periodontal infections	Tetracycline, 250 mg PO/6 h or 500 mg PO/bid Clarithromycin, 500 mg PO/day	Azithromycin, 500 mg PO/3 days
		Amoxicillin, 500 mg PO/bid/10 days
		Metronidazole, 250 mg PO/6–8 h/10 days or 500 mg PO/8 h/10 days
Oral candidiasis	Nystatin, 400,000–600,000 units PO/4 times a day after meals/7–14 days	Fluconazole, 100–200 mg PO once daily/7–14 days after clinical improvement
		Itraconazole, 200 mg PO day/7–14 days
Rhino-orbital or rhino-cerebral sinusitis	Amphotericin B, 0.25–0.3 mg/kg IV/24 h, increasing by 5–10 mg/day to a final dose of 0.5–0.7 mg/kg/day for 12 weeks	Posaconazole, oral solution, 800 mg in 4 divided doses/day for 12 weeks
		Posaconazole, oral solution, 800 mg in 4 divided doses/day
		Isavuconazole, 200 mg orally or IV, loading dose: 200 mg/8 h/2 days; 200 mg/day afterwards for 12 weeks
Influenza	Neuraminidase inhibitors	M2 Inhibitors
	Laninamivir one single inhalation of 20 mg for children <10 years, one single inhalation of 40 mg for individuals ≥10 years	Amantadine 100 mg/12 h/5 days
	Oseltamivir 75 mg/12 h/5 days	Rimantadine 100 mg/12 h/5 days
Community-acquired pneumonia	Outpatients: β-lactam (i.e., Amoxicillin 875–1000 mg/clavulanate, 62.5–125 mg PO/12 h) plus macrolide (i.e., Clarithromycin, 500 mg/day PO/5–10 days or Azithromycin, 500 mg/day PO/3 days) within 4–8 h after diagnosis	Respiratory fluoroquinolone: Moxifloxacin, 400 mg PO once daily/7–14 days
	Inpatients, non-ICU: Respiratory fluoroquinolone (i.e., moxifloxacin or levofloxacin PO or IV)	Levofloxacin, 500 mg PO once daily/10–14 days or 750 mg once daily/5–7 days or 750 mg IV/24 h/7 days
	Inpatients, ICU: A β-lactam (cefotaxime, ceftriaxone, ampicillin-sulbactam IV) plus azithromycin or respiratory fluoroquinolone (i.e., moxifloxacin, levofloxacin IV)	
	For penicillin allergic patients: a respiratory fluoroquinolone and aztreonam IM or IV	

Table 47.5 (continued)

Infection	First choice	Alternate choice(s)
Pulmonary tuberculosis	Short therapy for isoniazid sensitive TB: Isoniazid plus rifampicin PO for 6 months, plus ethambutol and pyrazinamide PO for the first 2 months	Long therapy for isoniazid mono-resistant TB: Rifampicin, ethambutol, and pyrazinamide for the first 6 months, or for 9 months with rifampicin, ethambutol, and pyrazinamide in the intensive phase and for two additional months with rifampicin and ethambutol in the continuation phase
Pulmonary coccidioidomycosis	Fluconazole, 800–1200 mg PO or IV/day	Amphotericin B, 5.0 up to 7.5–10.0 mg/kg/day IV for 12 weeks
	Inability of azoles to eradicate the fungus results in the need to continue treatment indefinitely as suppressive rather than curative therapy	Because of multiple adverse events, it should only be used in patients with refractory disease
Pulmonary mucormycosis	Amphotericin B, 5.0 up to 7.5–10.0 mg/kg/day IV for 12 weeks	Posaconazole, oral solution, 800 mg in 4 divided doses/day for 12 weeks
		Posaconazole, oral solution, 800 mg in 4 divided doses/day
		Isavuconazole, 200 mg orally or IV, loading dose: 200 mg/8 h/2 days; 200 mg/day afterwards for 12 weeks
Acute emphysematous cholecystitis	Ampicillin-sulbactam, 3 g/IV/6 h	Ampicillin 2 g/IV/6 h plus gentamicin 5 mg/kg/24 h plus clindamycin 900 mg/IV/8 h or Ceftriaxone 1–2 g IM or IV/24 h plus clindamycin or metronidazole, loading dose 15 mg/kg followed by 7.5 mg/kg IV/6 h
Pyogenic liver abscess	Multiple combination therapies have been used, including aminopenicillins, antipseudomonal penicillins, first-generation, second-generation, third-generation cephalosporins, carbapenems, fluoroquinolones, aminoglycosides, metronidazole	
Psoas and spinal epidural abscess	Nafcillin, 1000 mg IV/4 h or Oxacillin, 1000 mg/day IV every 4–6 h or Cefazolin, 100 mg/kg/day IM or IV/8 h	Ciprofloxacin 750 mg/12 h for 6 weeks
Asymptomatic bacteriuria	Screening and treatment unwarranted	
Asymptomatic candidiuria	Fluconazole, 400–800 mg PO, single dose	Caspofungin 70 mg IV loading dose → 50 mg/day
		Anidulafungin 200 mg/kg IV loading dose →100 mg/day
		Voriconazole 6 mg/kg IV/12 h; afterwards, 4 mg/kg/12 h
		Amphotericin B 0.6–0.7 mg/kg/day ± flucytosine 25 mg/kg/6 h/7–10 days
Bacterial pyelonephritis	Uncomplicated: Ciprofloxacin, 500 mg PO/bid/7 days or Tobramycin, 3–5 mg/kg IV/24 h/3 days	Uncomplicated: Levofloxacin, 250–500 mg PO/day/10 days or Ceftriaxone, 1 g/IV/24 h/3 days
	Complicated	Complicated
Emphysematous pyelonephritis	Prolonged antimicrobial therapy (i.e., Trimethoprim-sulfamethoxazole, 160/800 mg PO or IV/bid) for weeks or months plus additional surgical measures (see Table 47.5)	

(continued)

Table 47.5 (continued)

Infection	First choice	Alternate choice(s)
Bacterial cystitis	Uncomplicated: short course of antimicrobial therapy	Uncomplicated: Trimethoprim-sulfamethoxazole, 1600/800 mg/bid/3 days
	Amoxicillin, 500 mg PO/tid/7 days, or Amoxicillin/clavulanic acid, 500 mg PO/tid/7 days or Cephalexin, 250–500 mg PO/tid/7 days or Norfloxacin, 400 mg PO/bid/3 days	Nitrofurantoin, 50–100 mg/qid/7 days
	Complicated infections: prolonged antimicrobial therapy	Complicated
Fungal cystitis	Fluconazole, 400 mg IV/day/14 days	Flucytosine, 25 mg/kg/6 h/14 days or Amphotericin B 0.5–0.7 mg/kg/day/14 days
Perinephric abscess	Nafcillin, 1000 mg IV/4 h or Oxacillin, 1000 mg/day IV every 4–6 h or Cefazolin, 100 mg/kg/day IM or IV/8 h	Oxacillin, 1000 mg/day IV every 4–6 h or Cefazolin, 100 mg/kg/day IM or IV/8 h
Emphysematous cystitis	Fluoroquinolone (i.e., Levofloxacin 250 mg IV/24 h/10 days or 750 mg IV/5 days, or Moxifloxacin, 400 mg PO or IV once daily/5–14 days or Ceftriaxone, 1–2 g IM or IV/24 h/10–14 days)	Carbapenem (i.e., Cilastatin/Imipenem, 500 mg IV/6 h or 1000 mg IV/8 h) or Aminoglycoside (i.e., Gentamicin, 3 mg/kg IM or IV/8 h/day/10 days)
Vulvovaginal candidiasis	Uncomplicated: Clotrimazole, 200 mg intravaginally/3 days	Uncomplicated: Fluconazole, 150 mg, single dose
	Miconazole, 2 ovules at bedtime/3 days	Recurrent: Fluconazole, 150 mg/week/6 months
	Butoconazole, 500 mg vaginal tablet single dose	
	Recurrent: Fluconazole, 200 mg PO/8 h/1 week	
	If symptom free, fluconazole, 200 mg once a week from weeks 2 to 8, 200 mg every 2 weeks from months 3 to 6 and 200 mg every 4 weeks from months 7 to 12	
Balanoposthitis	Clotrimazole, 1–2% cream until symptoms subside	Patients with severe symptoms: Fluconazole, 200 mg single dose
Necrotizing fasciitis	Penicillin G, 24 million U IV/day plus clindamycin, 900 mg IV/8 h plus gentamicin, 5 mg/kg IV/day or Meropenem, 1 g IV/8 h plus clindamycin, 600 mg IV/8 h or lincomycin 600 mg IV/8 h	Ampicillin-sulbactam 1.5–3.0 g IV/6–8 h or Ceftriaxone, 2 g IV/24 h plus clindamycin, 900 mg IV/8 h
Fournier's gangrene	Triple antibiotic therapy including (1) a broad-spectrum penicillin or third-generation cephalosporin, (2) an aminoglycoside, (3) metronidazole or clindamycin	Alternatively, triple antibiotic therapy including (1) a broad-spectrum penicillin or third-generation cephalosporin, (2) an aminoglycoside, (3) chloramphenicol
		Vancomycin in patients infected with methicillin-resistant *S. aureus*
		Amphotericin B in patients with fungal infections
Diabetic hand syndrome	Triple antibiotic therapy to cover Staphylococcus, Gram-negative organisms and anaerobes, including (1) third-generation cephalosporin, (2) aminoglycoside, (3) metronidazole or clindamycin	Second choice therapy based on results of wound swab and culture
Cellulitis	Amoxicillin-clavulanate	Third-generation cephalosporin with or without aminoglycoside
	First-generation cephalosporin	
	Macrolides	
	Fluoroquinolone	
	Ceftriaxone	

Table 47.5 (continued)

Infection	First choice	Alternate choice(s)
Foot ulcer infections	Mild to moderate: Amoxicillin-clavulanate, 875/125 mg PO/12 h or Ampicillin/sulbactam, 3 g IV/6 h	Mild to moderate: Cephalexin, 500 mg PO/6 h plus metronidazole, 400 mg PO/8–12 h or Ciprofloxacin, 500 PO/12 h plus clindamycin, 300–450 mg PO/8 h or 600 mg IV/8 h
	Severe: Ticarcillin-clavulanate, 0.1–0.3 g IV/h or Meropenem-cilastatin 500 mg IV/8 h	Severe: Ciprofloxacin, 750 mg VO/12 h plus clindamycin, 600 mg IV/8 h or lincomycin, 600 mg IV/8 h
Herpes zoster	Acyclovir, 800 mg PO/5 times a day/7–10 days	Famciclovir, 500 mg PO/7 days
		Valacyclovir, 1000 mg/tid/7 days
Onychomycosis	Terbinafine, 250 mg/day PO/12 weeks	Itraconazole, 200 mg/bid/1 week on, 3 weeks of/12 weeks
	Use with caution in patients with liver or kidney disease	Contraindicated in patients with congestive heart failure
	Fluconazole, 150, 300, or 450 mg PO/week/6 months	
Cutaneous zygomycosis	Amphotericin B, 5.0 up to 7.5–10.0 mg/kg/day IV for 12 weeks	Posaconazole, oral solution, 800 mg in 4 divided doses/day for 12 weeks
		Posaconazole, oral solution, 800 mg in 4 divided doses/day
		Isavuconazole, 200 mg orally or IV, loading dose: 200 mg/8 h/2 days; 200 mg/day afterwards for 12 weeks

Table 47.6 Choice of antimicrobial therapy by microorganisms and dose in adults

	First line, dose, and duration		Second line, dose, and duration	
Microorganism	Oral	Intramuscular or intravenous	Oral	Intramuscular or intravenous
Bacteria				
Streptococcus pneumoniae	β-lactam	Benzylpenicillin 1.2 g IV/6 h	Respiratory fluoroquinolone: Moxifloxacin, 400 mg PO once daily/7–14 days	Vancomycin, 25–30 loading dose for seriously ill patients, then 15–20 mg/kg IV/8–12 h in combination FDA approved labeling: 2 g/day IV divided either as 500 mg IV/6 h or 1 g IV/12 h
	(Amoxicillin, 500–875 mg) plus macrolide	Cefuroxime, 750–1500 mg IV/8 h; for life-threatening infections, 1.5 g IV/6 h	Gemifloxacin, Levofloxacin, 500 mg PO once daily/10–14 days or 750 mg once daily/5–7 days or 750 mg IV/24 h/7 days	Linezolid, 600 mg IV/12 h/10–14 days. Duration of treatment is 7–21 days for methicillin-resistant *Staphylococcus aureus*
	(Clarithromycin, 500 mg/day) within 4–8 h after diagnosis	Cefotaxime, for uncomplicated infections: 1 g IM or IV/12 h, for complicated infections, 2 g IV/6–8 h/7–10 days		
		Ceftriaxone, 1–2 g IM or IV/day/7–10 days, depending on clinical response		
Haemophilus influenza	Amoxicillin-clavulanate, 500–875 mg/8–12 h	Respiratory fluoroquinolone: Moxifloxacin, 400 mg PO once daily/7–14 days	Doxycycline, 100 mg/12 h day	Respiratory fluoroquinolone: Levofloxacin, 750 mg IV/24 h/7 days
		Levofloxacin, 500 mg PO once daily/10–14 days or 750 mg once daily/5–7 days	Azithromycin, 200 mg/day	
			Clarithromycin, 500 mg/day	

(continued)

Table 47.6 (continued)

	First line, dose, and duration		Second line, dose, and duration	
Microorganism	Oral	Intramuscular or intravenous	Oral	Intramuscular or intravenous
Staphylococcus aureus	Dicloxacillin, 125–250 mg PO/6 h for moderate infections, 250–500 mg PO/6 h for severe infections	Nafcillin, 500 mg IV/4 h for moderate infections, 1000 mg IV/4 h for severe infections	Clindamycin, 150–450 mg PO/6 h	Clindamycin, 600 mg IM or IV/6–12 h up to 900 mg/8–12 h
		Oxacillin, 1 g/day IV every 4–6 h		Vancomycin, 25–30 loading dose for seriously ill patients, then 15–20 mg/kg IV/8–12 h in combination FDA approved labeling: 2 g/day IV divided either as 500 mg IV/6 h or 1 g IV/12 h
		Cefazolin, 250–500 mg/kg/IM or IV/8 h for mild to moderate infections; 100 mg/kg/day IM or IV divided every 8 h for severe infections		Linezolid, 600 mg IV/12 h/10–14 days
Mycoplasma pneumoniae	Clarithromycin, 500 mg/day	Respiratory fluoroquinolone: Moxifloxacin, 400 mg PO once daily/7–14 days		
		Levofloxacin, 500 mg PO once daily/10–14 days or 750 mg once daily/5–7 days		
Mycobacterium tuberculosis	Short therapy for isoniazid-sensitive TB: Isoniazid plus rifampicin for 6 months, plus ethambutol and pyrazinamide for the first 2 months		Long therapy for isoniazid mono-resistant TB: Rifampicin, ethambutol, and pyrazinamide for the first 6 months, or for 9 months with rifampicin, ethambutol, and pyrazinamide in the intensive phase and for two additional months with rifampicin and ethambutol in the continuation phase	
Legionella sp.	Respiratory fluoroquinolone, i.e., Moxifloxacin, 400 mg PO once daily/7–10 days or Levofloxacin, 750 mg PO once daily/5–10 days		Azithromycin, 1000 mg PO/day followed by 500 mg/day/10 days or Doxycycline, 100 mg PO/day	
Klebsiella pneumoniae		Ertapenem, 1 g IM or IV/24 h/10–14 days		Avibactam/Ceftazidime, 2.5 g (2 g Ceftazidime, 0.5 g Avibactam) IV/8 h/7–14 days
		Imipenem-Cilastatin, 1 g IV/6–8 h		
		Meropenem, 1 g IV/8 h		
Escherichia coli		Ertapenem, 1 g IM or IV/24 h/10–14 days		Aminoglycosides, i.e., Amikacin, 15 mg/kg/day IM or IV/8–12 h or Gentamicin, 3 mg/kg IM or IV/day/divided in three doses/10 days or Tobramycin, 3–6 mg/kg IM or IV/day divided in 2–3 doses
		Imipenem-Cilastatin, 1 g IV/6–8 h		
		Meropenem, 1 g IV/8 h		

Table 47.6 (continued)

First line, dose, and duration			Second line, dose, and duration	
Microorganism	Oral	Intramuscular or intravenous	Oral	Intramuscular or intravenous
Acinetobacter		Ertapenem, 1 g IM or IV/24 h/10–14 days		Aminoglycosides, i.e., Amikacin, 15 mg/kg/day IM or IV/8–12 h or Gentamicin, 3 mg/kg IM or IV/day/divided in three doses or Tobramycin, 3–6 mg/kg IM or IV/day divided in 2–3 doses
		Imipenem-Cilastatin, 1 g IV/6–8 h		Third-generation Cephalosporins, including Cefotaxime, 1–2 g IM or IV/12 h
		Meropenem, 1 g IV/8 h		Ceftriaxone 1–2 g IM or IV/24 h
				Avibactam/Ceftazidime, 2.5 g (2 g Ceftazidime, 0.5 g Avibactam) IV/8 h
				Ampicillin-sulbactam, 1.5 g (1 g ampicillin and 0.5 g sulbactam) IM or IV/6 h
Pseudomonas aeruginosa	Levofloxacin, 250–750 mg PO/day	Cefepime, 0.5–1.0 g IM or IV or Ciprofloxacin 400 mg IV/12 h or Aztreonam, 500–1000 mg IM or IV/8–12 h		Ticarcillin-clavulanate 3.0–0.1 g IV/6 h or third-generation cephalosporin, i.e., Ceftazidime 2 g IV/8 h plus Aminoglycoside, i.e., Gentamicin, 4–6 mg/kg IV day
		Carbapenem, i.e., Imipenem/cilastatin 500–1000 mg IV/6–8 h or Meropenem, 1 g IV/8 h		Ciprofloxacin 1.5 g/day or Levofloxacin, 500 mg IV/day or Ticarcillin, 3.1 g (3 g ticarcillin and 0.1 g clavulanic acid) IV/4–6 h or Piperacillin/tazobactam, 3.375 g (3 g piperacillin and 0.375 tazobactam) IV/6 h
Fungi				
Rhizopus and *Mucor*	Amphotericin B, 5 mg/kg/day IV for 12 weeks		Posaconazole, oral solution, 800 mg in 4 divided doses/day for 12 weeks for patients who cannot tolerate or non-responders to Amphotericin B	
Candida	Oral: Nystatin 100,000 units/mL after meals	Toenail: Itraconazole, 200 mg once daily/12 weeks	Fluconazole 200 mg day/3 days	Itraconazole 200 mg day
	Toenail: Terbinafine, 250 mg once daily/12 weeks	Topical: Ciclopirox, once daily application, avoiding washing for 8 h after application		
		Efinaconazole, once daily application for 48 weeks		
		Tavaborole, once daily application for 48 weeks		

(continued)

Table 47.6 (continued)

	First line, dose, and duration		Second line, dose, and duration	
Microorganism	Oral	Intramuscular or intravenous	Oral	Intramuscular or intravenous
Aspergillus		Amphotericin B 2 g day IV/3 weeks for invasive Aspergillosis	Voriconazole 200 mg day/6 weeks, for invasive Aspergillosis	
Histoplasma capsulatum	Itraconazole	Amphotericin B 2 g day IV/3 weeks		Amphotericin B 2 g day IV/3 weeks
Coccidioides	Fluconazole, 800–1200 mg/day	Amphotericin B 2 g day IV/3 weeks for invasive Coccidioidomycosis	Voriconazole 200 mg day/6 weeks, for invasive Coccidioidomycosis	
	Warning: inability of azoles to eradicate the fungus results in the need to continue treatment indefinitely as suppressive rather than curative therapy		Posaconazole, oral solution, 800 mg in 4 divided doses/day for 12 weeks for patients who cannot tolerate or non-responders to Amphotericin B	
Viruses				
Influenza	M2 Inhibitors			
	Amantadine 100 mg/12 h/5 days			
	Rimantadine 100 mg/12 h/5 days			
	Neuraminidase inhibitors			
	Laninamivir one single inhalation of 20 mg for children <10 years, one single inhalation of 40 mg for individuals ≥10 years			
	Oseltamivir 75 mg/12 h/5 days			
Herpes zoster	Acyclovir, 800 mg 5 times a day, 7–10 days		Famciclovir, 500 mg 3 times a day, 7–10 days	
	In patients with persistent varicella DNA in the cornea, antiviral therapy may extend up to 30 days		In patients with persistent varicella DNA in the cornea, antiviral therapy may extend up to 30 days	
			Valacyclovir, 1 g 3 times a day, 7–10 days	
			In patients with persistent varicella DNA in the cornea, antiviral therapy may extend up to 30 days	

and second option choices of antibacterials, antimycotics, and antivirals. Microorganisms showing increasing rates of antimicrobial resistance like Pseudomonas and Acinetobacter are effectively treated combining two antibiotics. Diabetic foot infections, skin and soft tissue infections, periodontitis along with emphysematous cholecystitis often require polymicrobial cover, especially to include anaerobes.

Glycemic Control

Poor glycemic control, especially in the presence of infection, can lead to metabolic and infection-related complications. Insulin requirements may increase during infections. Insulin is an anabolic agent, and it should be the preferred drug for glycemic control in the background of infection.

Source Control

Source control in the form of drainage or debridement of the infective focus can lead to reduction in the bacterial load, help achieve better glycemic control, and reduce the risk of complications. In addition to antimicrobials, complementary interventions for selected infections are presented in Table 47.7.

Table 47.7 Additional therapeutic measures and prognosis

Disease	Therapeutic measure	Prognosis
Herpes zoster ophthalmicus	• Oral or topical corticosteroids	Complications related to bad prognosis: Meningitis, brain abscess, dural sinus thrombophlebitis
	• Frequent artificial tears	
	• Monitoring for signs of secondary bacterial infection	
	• Prophylactic erythromycin ophthalmic ointment	
	• Analgesics in the acute phase and in patients with post-herpetic neuralgia	
Malignant external otitis	• Six weeks or longer of culture-directed antibiotic therapy, based on the 3–4-week period for bone revascularization	Reported mortality rates in recent series is 30%
	• Otolaryngology management	More aggressive strains and increasing antibiotic resistance are requiring multidrug and long-term antibiotic therapy with extended hospital stays
	• Repeated debridement of the ear, the infratemporal fossa, or skull base	Signs of disease progression and poor outcomes:
	• Radical mastoidectomy with facial nerve decompression	Lack of glycemic control
		Cranial nerve involvement
		Extension to the jugular foramen and petrous apex
		Erythrocyte sedimentation rate
		C-Reactive protein
		Causes of death:
		Meningitis, large vessel septic thrombophlebitis or rupture, septicemia, pneumonia, stroke
		Predictors of symptom resolution for fungal malignant external otitis:
		No surgical debridement
		Absence of facial paralysis
		Aspergillus as causative pathogen
		Absence of imaging findings
		Indicator of disease resolution: negative results by Ga-67 citrate scan
Periodontal infections	Systemic antibiotics are important, but only in addition to reducing the bacterial load with periodontal scaling and root planning	Because of increasing resistance, combinations of antibiotics are increasingly used
Oral candidiasis	Glycemic control	
	Oral hygiene	
	Avoiding tobacco use	
Rhino-orbital mucormycosis	Surgical debridement of infected tissue, including removal of the palate, nasal cartilages, and orbit as soon as possible, is crucial to prevent dissemination	Mortality rate: 25–62%
		Poor outcome predictors: dissemination, renal failure, inability to achieve source control, brain or cavernous sinus involvement, lack of response to antifungals
Influenza	In addition to diabetes, higher risks of complications occur in children, the elderly, and pregnant	Worldwide mortality rate for influenza from subgroups H5N1 and H7N9 of influenza A virus: 53% and 39%

(continued)

Table 47.7 (continued)

Disease	Therapeutic measure	Prognosis
Community-acquired pneumonia	Recommended actions to improve the outcomes include: (1) using a risk stratification tool like CURB-65 (confusion, urea >7 mmol/L, respiratory rate ≥30/min, low blood pressure, and older than 65), (2) procalcitonin to confirm diagnosis and assess treatment response, (3) outpatient treatment, (4) use of empirical antibiotic guidelines in accordance to local microbial etiology, (5) measure time to achieve clinical stability, step-down to oral antibiotics, early physical therapy, patient and caregiver education, appropriate venous thromboembolism prophylaxis	Odds ratio for pneumonia: 1.5
	Criteria to transition from intravenous to oral therapy: (1) absence of mental confusion, (2) ability to take oral medications, (3) hemodynamic stability (heart rate <100 beats/min, systolic blood pressure >90 mmHg), (4) respiratory rate <25 breaths/min, (5) oxygen saturation >90%	Hazard ratio for pneumonia: 2.9
	Administration of macrolides before beta-lactams is associated with a statistically significant decrease in mortality, even in hospitalized patients. Data from many countries show an increased prevalence of macrolide-resistant *Streptococcus pneumonia*. For example, in the United Sates the overall rate of macrolide-resistant *S. pneumoniae* is 50%. Nevertheless, resistance does not automatically mean treatment failure. Another important factor is the increasing awareness of respiratory viruses and atypical species as co-pathogens	Risk of invasive pneumococcal disease: 1.4–4.6, especially in individuals younger than 40 years
		Odds ratio for bacteremia: 1.67
		Hyperglycemia is independently associated with adverse outcomes in patients with community-acquired pneumonia
		Preexisting diabetes and newly discovered hyperglycemia are associated with a higher risk of death, for several years. A pre-pneumonia diagnosis of diabetes is associated with a threefold increase in the risk of death up to 6 years after mild to moderate community-acquired pneumonia.
		Rather than disruption of the immune response, death may be related to worsening of preexisting cardiovascular and kidney disease
Tuberculosis	Although treatment schedule can be as high 95–98% under clinical trial conditions (directly observed therapy or DOT), high rates of non-adherence after 4 weeks of therapy (between 7% and 53.6%) are common. Therapeutic drug monitoring has been proposed to optimize treatment outcome and reduce drug resistance	Patients with diabetes are at a higher risk of developing active tuberculosis, drug-resistant disease, treatment failure, and mortality
	Drug-induced liver injury may be caused by isoniazid, rifampicin, or pyrazinamide, in the range of 5–33%	Compared with patients without diabetes, the risk of active tuberculosis is 1.55–3.59 higher
	Treatment of multidrug-resistant tuberculosis includes: (1) at least four drugs with proven or likely susceptibility, (2) a later generation fluoroquinolone (moxifloxacin, levofloxacin), plus an aminoglycoside (amikacin, kanamycin, capreomycin), (3) long duration of treatment (21–24 months), (4) oxazolidinones (linezolid) with monitoring for neuropathy and bone marrow toxicity, in patients with fluoroquinolone-resistant TB, (5) bedaquiline or delamanid for patients with toxicity or resistance to multidrug regimens, (6) psychological and economic support	Tuberculosis prevalence and incidence are more likely to increase in countries where diabetes prevalence has increased
		Death rates: for untreated smear-positive TB: 70%, for smear negative TB: 20%
		Patients with diabetes and tuberculosis have: (1) significantly higher rates of treatment failure and death; (2) higher risk of death during treatment and relapse following treatment; (3) remain sputum positive 2–3 months after starting TB treatment.
		Infection and treatment for tuberculosis impair glycemic control and peripheral neuropathy in patients receiving isoniazid

Table 47.7 (continued)

Disease	Therapeutic measure	Prognosis
Coccidioidomycosis	Exogenous adjunctive interferon-γ has been used in patients with chronic coccidioidomycosis, in addition to antifungal therapy	The disease is relatively benign in most cases but for others is debilitating and may be mortal
	Nikkomycin has shown promise as a cure in murine models of infection	Recurrence is possible in patients with benign disease
		Extrapulmonary disease occurs through hematogenous or lymphatic spread and may involve meninges, skeleton, skin, joints, glandular tissue, peritoneum, liver, pancreas, pericardium, bone marrow, kidney, bladder, and male and female reproductive organs
		In these cases treatment is prolonged, even for years with close follow-up for relapses
Emphysematous pyelonephritis	Percutaneous drainage	Delayed nephrectomy if necessary, once the patient is stable
Psoas abscess	Surgical drainage	Mortality 17%, for primary psoas abscess: 2.5%, for secondary psoas abscess: 18.9%
		Death largely related to comorbidities, delayed diagnosis, or inadequate therapy
Perinephric abscess	Percutaneous drainage	Percutaneous nephrolithotomy in case of infective stone
		In patients with chronic abscess, nephrectomy
Fungal urinary tract infections	Correct predisposing factors, including: (1) removal of indwelling devices, (2) improving urinary tract drainage, (3) discontinue systemic antibiotics, (4) treating underlying medical problems	Glycemic control is essential
		Strategies to reduce funguria include: (1) adequate hydration, (2) hygiene, (3) vaginal estrogens
Emphysematous cystitis	90% of cases are treated with medical treatment alone, 10% require medical and surgical intervention, including: bladder drainage, surgical debridement, partial cystectomy, total cystectomy, or even nephrectomy	Death rate: 7–12% from septic shock or late presentation
Necrotizing fasciitis	Surgical debridement of necrotic tissue is essential for recovery	
Fournier's gangrene	Early and aggressive surgical debridement improves survival	Wide reported mortality rate: 4.0–88.0%
	Additional interventions include negative-pressure wound therapy, hyperbaric oxygen therapy, fecal and urinary diversion, and reconstructive surgery	
Diabetic hand syndrome	Comprehensive management include: (1) hospitalization and hand elevation, (2) multiple intravenous antibiotics, (3) optimal glycemic control, (4) adequate and early surgical drainage, (5) prompt amputation if necessary, (6) rehabilitation	Life expectancy of high upper limb amputees may be lower, but the number of reported cases is low to be conclusive
Cellulitis	Most cases improve within 1 day, but thickening of the debris requires parenteral antibiotics before improvement	Recurrent cellulitis can compromise venous or lymphatic circulation and result in dermal fibrosis, lymphedema, and epidermal thickening
	Adjunctive treatment includes cool compresses, analgesics, and immobilization of the affected extremity	Prophylaxis with erythromycin, penicillin, or clindamycin is indicated in these cases

(continued)

Table 47.7 (continued)

Disease	Therapeutic measure	Prognosis
Foot ulcer infections	For mild to moderate infections, antimicrobial therapy for 1–2 weeks is adequate	Factors predicting healing include: (1) absence of exposed bone, (2) palpable pedal pulses, (3) blood pressure in the toe >45 mmHg or >80 mmHg in the ankle, (4) peripheral white cell count <12,000/mm^3, (5) lower extremity transcutaneous oxygen tension >40 mmHg
	Most severe infections and some moderate require parenteral antimicrobial therapy for 1–2 weeks with a switch to oral therapy according to clinical response	Failure to treat diabetes foot infections is associated with progressive tissue destruction, poor wound healing, amputation, sepsis, and death
	Patients with osteomyelitis not undergoing resection require 6 weeks of antimicrobial therapy	Beyond intervention, healthcare practitioners should focus on prevention in patients at high risk for diabetic foot ulcers
	Patients with osteomyelitis undergoing resection require 1 week of antimicrobial therapy	
	Urgent surgical intervention by certified specialists is necessary in case of deep abscess, compartment syndrome, and necrotizing soft tissue infections	
	Surgical intervention is advisable in cases of osteomyelitis associated with spreading soft tissue infection, destroyed soft tissue envelope, progressive bone destruction, or bone protruding through an ulcer	
Herpes zoster	Complications include post-herpetic neuralgia and secondary bacterial infections; less common complications are neurologic, and include aseptic meningitis, peripheral motor neuropathy, transverse myelitis, acute or chronic encephalitis, Guillain-Barré syndrome, and stroke symptoms resulting from vasculitis of cerebral arteries	Post-herpetic neuralgia is the most common complication; risk factors include advanced age and severity of rash and pain
Onychomycosis	Nail lacquers are an attractive option and include 8% ciclopirox, once daily/48 weeks and 5% amorolfine, once or twice weekly/6 months	Risk factors for *Candida* onychomycosis include peripheral vascular disease and female gender. Consider this diagnosis in patients with onycholysis, paronychia, or total dystrophic onychomycosis
	Unattached infected nail should be removed once a month	Onychomycosis is a significant predictor for the development of foot ulcers
	Filing of excess horny material should be done by trained professionals	Rates of mycological cure are low: 31% with azoles, 57% with terbinafine
	Patients should file away loose nail material and trim nails as directed by podologists, or every 7 days after weekly removal of medication with alcohol	
Cutaneous zygomycosis		

When to Refer

Any case which appears complex to the treating physician may be referred to a specialist. However priority referrals should be considered in case of diabetes complicating pregnancy, renal impairment, diabetic foot, life-threatening invasive mucormycosis, and coronavirus-19.

Conclusion

Hyperglycemia is associated with disorders in the immune system including lower secretion of inflammatory cytokines, impairment in neutrophile, humoral and T cell function, increased susceptibility, and delayed recovery of tissues [24]. Awareness of microvascular and macrovascular complications can help minimize the risk of infections and infection-related complications. Healthcare personnel need to be aware of unusual and severe forms of infection associated with diabetes mellitus. The use of empirical antibiotics is the same as with non-diabetics, but disease-associated complications should be anticipated and promptly treated. Immunization with influenza and pneumococcal vaccine is often recommended. Optimal glycemic control is essential for successful treatment of infections.

Multiple-Choice Questions

1. This class of drugs is associated with a higher risk of pruritis vulvae/balanoposthitis:
   (a) **SGLT2i**
   (b) Pioglitazone
   (c) Biguanides
   (d) Sulfonylureas
2. This class of drugs has an anabolic effect and is the preferred agent for glycemic control in the background of infection:
   (a) **Insulin**
   (b) GLP1RA
   (c) DPP4i
   (d) Bromocriptine
3. This parasitic infection may protect against diabetes:
   (a) **Helminthiasis**
   (b) Malaria
   (c) Mucormycosis
   (d) Lichen planus
4. Hypoglycemia may occur in all of the following setting, except
   (a) **Dengue fever**
   (b) Malaria
   (c) Insulin use
   (d) Quinine use
5. Anaerobic bacterial coverage is indicated in all of the following settings except
   (a) **Pyogenic meningitis**
   (b) Lung abscess
   (c) Infected diabetic foot
   (d) Emphysematous pyelonephritis
6. The causative organism of otitis externa is
   (a) *Klebsiella* sp.
   (b) Proteus
   (c) *Staphylococcus aureus*
   (d) **All of the above**
7. This infection is not associated with a higher risk of diabetes:
   (a) **Hepatitis A**
   (b) Tuberculosis
   (c) HIV
   (d) Hepatitis C
8. This antimicrobial drug may precipitate hypoglycemia:
   (a) **Gatifloxacin**
   (b) Azithromycin
   (c) Metronidazole
   (d) Streptomycin
9. Hyperglycemia increases the risk of COVID-19 infection because of
   (a) Oxidative stress
   (b) Inflammation
   (c) Apoptosis of alveolar cells
   (d) None of the above
   (e) **All of the above**
10. Glycemic threshold for high risk of severity and mortality from COVID-19 infection:
   (a) 120 mg/dL
   (b) 140 mg/dL
   (c) **180 mg/dL**
   (d) 200 mg/dL
   (e) 250 mg/dL

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COVID-19, Diabetes, and Cardiovascular Disease

48

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Pathogenesis

People with chronic-degenerative diseases usually present severe COVID symptoms, as well as a higher risk of postinfection complications. These comorbidities modify metabolism by increasing the expression of the enzyme ACE-2 in infected people. ACE-2 encodes the protein through which the virus enters the cell, so the increased production of ACE-2 in patients with these diseases facilitates the entry of SARS-CoV-2 [1] and induces a great deal of impact on underlying conditions, complications of infections, and other diseases [2, 3]. It has also been observed that COVID-19 infection leads to the worsening of conditions in the presence of CVD [4, 5]. Epidemiological studies have indicated that patients with DM and COVID-19 infection require more medical interventions, have higher mortality rates [7.8% versus 2.7%, adjusted hazard ratio (HR) 1.49], and have a greater frequency of multiple-organ damage than those without DM [6].

Epidemiology

Across the United States, there were 95,235 reported deaths officially attributed to COVID-19 from March 1 to May 30, 2020. By comparison, there were an estimated 122,300 (95% prediction interval, 116,800–127,000) excess deaths during the same period. Even in situations of ample testing, deaths due to viral pathogens, including SARS-CoV-2, can occur indirectly via secondary bacterial infections or exacerbation of comorbidities, mainly CVD [7, 8]. A study published in Italy compared excess deaths from CVD and excess deaths due to the new coronavirus. The trajectory of the number of excess deaths from CVD was highly parallel to the trajectory of the number of excess deaths related to COVID-19. The number of excess deaths from DM, influenza, respiratory diseases, and malignant neoplasms remained relatively stable over time. The parallel trajectory of excess mortality from CVD and COVID-19 over time reflects the fact that essential health services for noncommunicable diseases were reduced or disrupted during the COVID-19 pandemic, and the more severe the pandemic, the heavier the impact. Many European countries have experienced sharp increases in all-cause deaths associated with the pandemic [9].

DM is associated with an increased risk of infections, especially infections of the skin and urinary and respiratory tracts. This is due to immunological dysfunction secondary to the hyperglycemic milieu of people with DM [10]. Bacterial and fungal infections have a higher incidence in patients with DM, albeit previous studies do not associate DM with an increased incidence in viral infections such as COVID-19 [11]. Nevertheless, a meta-analysis of six Chinese studies including 1527 patients hospitalized with COVID-19 demonstrated significant differences in the prevalence of hyperglycemia in severe versus non-severe cases, in addition to a prevalence of DM of 11.7% in ICU cases, in comparison with 4.0% in non-ICU cases [12]. In line with these findings, a report from the Chinese Center for Disease Control and Prevention on 44,672 COVID-19 cases, which also included nonhospitalized patients, showed a lower prevalence of DM (5.3%). But it is associated with poor prognosis [12]. A meta-analysis with 6452 patients from 30 studies showed that DM was associated with a compound poor outcome (RR 2.38 [1.88, 3.03], $p < 0.001$; I^2, 62%) [13]. A group of researchers from Mexico published an article proposing a mechanistic approach to evaluate the risk for complications and lethality attributable to COVID-19 in which they included early-onset diabetes, obesity, chronic obstructive pulmonary disease, advanced age, hypertension, immunosuppression, and chronic kidney disease [14]. Among these variables, the results of this study showed that early-onset diabetes conferred an increased risk of hospitalization and obesity conferred an increased risk for intensive care admission and intubation [14].

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Management of Diabetes, COVID-19, and Cardiovascular Disease

The management of DM in patients with COVID-19 infection has a remarkable impact on the mortality from this disease, according to the fact that patients with better control have fewer complications in comparison with the ones who are not in control [15]. General recommendations for DM management include increasing physical activity as part of the treatment. A study suggested that physical inactivity is correlated with a higher relative risk of COVID-19 hospitalization, even after controlling for age, sex, obesity, smoking, and alcohol intake [RR, 1.32 (95% confidence interval [CI], 1.10–1.58)] [16]. It is expected that inactivity or a sedentary lifestyle will increase to produce 11 million new patients debuting with DM2 and up to almost 2 million deaths related to metabolic syndrome leading to decreased physical activity and increased prevalence of obesity [17]. Strategies to avoid physical inactivity and reduce stress levels can promote cardiovascular protection. The promotion of physical activity is prioritized by public health agencies and has been incorporated into routine medical care [18]. A home-based training protocol could be an important and effective strategy for individuals who need to remain safe and physically active.

International guidelines have already standardized the use of a glucocorticoid, anti-inflammatory drug therapy, and prophylactic anticoagulant in patients with COVID-19 [19]. For this reason, frequent glucose monitoring in DM patients and COVID-19 is imperative. A relevant study by Lu et al. supports that less variability in glucose excursions measured as time in range was associated with a lower risk of all-cause mortality and cardiovascular mortality among patients with type 2 DM [20] . Many patients previously on oral hypoglycemic agents will require conversion to insulin during hospitalization; in severe cases of COVID-19, insulin requirements are extremely high; these patients had a worse prognosis, compared with their counterparts who had not received insulin. This finding is probably secondary to the hyperinflammatory state on insulin resistance, reflecting that insulin treatment is a marker for advanced DM [21]. The results of this review indicate that there is no reason to cease the use of antidiabetic medications, that long-term glycemic control is essential in patients with COVID-19, and that it can improve the prognosis in these patients. Although potential direct therapeutic benefits have been proposed, the safety of some glucose-lowering therapies is still questioned [22]. An observational cohort study in England to investigate the association between prescription of different classes of glucose-lowering drugs and risk of COVID-19 mortality in a population of almost three million people with type 2 diabetes showed the following hazard ratios (HR): 0.77 for metformin, 1.42 for insulin, 0.75 for meglitinides, 0.82 for SGLT2 inhibitors, 0.94 for glitazones, sulfonylureas and GLP-1 receptor agonists, 1.07 for DPP inhibitors, and 1.26 for α-glucosidase inhibitors [23]. The study provides compelling evidence about the associations of some prescription drugs, although the differences are small and likely due to confounding [23].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have raised high expectancies because of their cardioprotective effects. The EMPA-REG OUTCOME, a randomized, double-blind, placebo-controlled trial that evaluated the effect of empagliflozin, found a significant reduction in major adverse cardiovascular outcomes including cardiovascular death, myocardial infarction, or stroke, as well as death from cardiovascular causes, death from any cause, progression of renal disease, and hospitalization for heart failure (HF) [24]. These findings were confirmed in the DAPA-HF trial in which 4744 patients with HF and a reduced ejection fraction were randomly assigned to receive either dapagliflozin or placebo in addition to standard HF therapy [25]. Of the enrolled patients, 41.8% had DM and the primary outcome of cardiovascular death or worsening HF was significantly lower in the dapagliflozin group than in the placebo group (16.3% vs. 21.2%; hazard ratio, 0.74; 95% confidence interval [CI], 0.65 to 0.85; *P* 0.001) [25]. This effect was not attributable to its low antihyperglycemic or natriuretic effects. Ferrannini et al. and Mudaliar et al. postulated that the action of SGLT2 inhibitors to promote ketogenesis might account for their favorable effects on the heart and kidney since enhanced ketone bodies' formation might provide an efficient fuel that could increase the energy status of organs under stress [26]. This effect would explain why this benefit is observed in patients with HF without DM. The DARE-19 trial, a randomized, double-blind, placebo-controlled trial, suggested that the SGLT2 inhibitor dapagliflozin was safe and well tolerated in patients hospitalized with COVID-19 with at least one cardiometabolic risk factor [27]. This study excluded critically ill patients, however, and did not result in a significant risk reduction in organ dysfunction or death nor an improvement in clinical status [27]. Currently there is a strong rationale to avoid treatment with metformin or SGLT2 inhibitors in patients with severe COVID-19 to reduce the risk of lactic acidosis, ketoacidosis, and volume depletion associated with the use of these drugs in the presence of severe infection [21].

Cardiovascular Complications of COVID-19 Infection

The symptoms and clinical course of COVID-19 are broad, ranging from asymptomatic to severe respiratory failure requiring mechanical ventilation. Metabolic and cardiovascular comorbidities have an important role in outcomes of patients with COVID-19 infection [15]. A meta-analysis of

six published studies from China including 1527 patients with COVID-19 reported a 9.7%, 16.4%, and 17.1% prevalence of DM, cardio-cerebrovascular disease, and hypertension, respectively [11], and the increasing knowledge of COVID-19 has provided a clearer picture of its clinical evolution: The first phase is asymptomatic or primarily characterized by symptoms in the upper respiratory tract; approximately 80% of the cases are resolved. The second phase, or moderate pneumonia, occurs approximately in 15%, requiring supplementary oxygen. About 5% evolve to the third phase, or severe pneumonia, with worsening of the respiratory condition, hypoxemia, fever, and acute respiratory distress syndrome [28]. In addition to respiratory symptoms, many patients have cardiovascular symptoms, such as heart palpitations and chest tightness/pain, as the initial clinical manifestation of COVID-19 [29]. When the cardiovascular system is affected, a wide range of complications can occur, from myocardial injury and acute myocardial infarction to heart failure, myocarditis, dysrhythmias, and venous thromboembolic events [28].

Regardless of the phases in which the patient has been through, moreover, several studies also showed that COVID-19 can exacerbate preexisting cardiovascular disease and/or cause new cardiovascular injuries [30]. Increased risk for myocardial infarction, fulminant myocarditis rapidly evolving with depressed systolic left ventricle function, arrhythmias, venous thromboembolism, and cardiomyopathies mimicking STEMI presentations are the most prevalent cardiovascular complications described in patients with COVID-19 [31].

The hypothesis of the cumulative effect of previous CV disease and troponin increase was postulated due to the greater presence of ACE2 receptors in postmortem cardiac pericytes extracted from patients with heart disease compared with those without the previous disease. That explains the affinity to this system [32]. Shi et al. reported that myocardial injury may be caused by myocarditis and myocardial ischemia, which is mainly manifested by elevated troponin levels, and higher mortality rates than those in people without myocardial injury (51.2% vs. 4.5%; $p < 0.001$), being an independent risk factor for mortality [33]. Myocardial injury has also been described in 5 of the first 41 patients diagnosed with COVID-19 in Wuhan, China, with elevated serum high-sensitivity cardiac troponin I (hs-ctni) levels (>28 ng/l) [34]. However, in a cohort study of 1597 US-competitive athletes with CMR screening after COVID-19 infection, 37 (2.3%) were diagnosed with clinical and subclinical myocarditis. If cardiac testing was based on cardiac symptoms alone, only 5 athletes would have been detected for a prevalence of 0.31% [35]. Regardless of the actual incidence, acute cardiac injury has been consistently shown to be a strong negative prognostic marker in patients with COVID-19 [35].

Heart failure is an important cause of death in patients with COVID-19 and occurs as a result of different myocardial aggression mechanisms such as direct myocardial injury by viral action, indirect and direct inflammatory damage, an imbalance in oxygen supply-demand, and an increase of atherothrombotic events due to inflammatory destabilization of atheromatous plaques, which result in acute myocardial dysfunction [36]. A clinical study of 99 cases with confirmed COVID-19 from Wuhan showed that 11 (11%) patients had died, of which 2 patients had no previous history of chronic heart disease but developed heart failure and eventually died of sudden cardiac arrest [37]. Even in the absence of direct myocardial injury, patients develop disturbances in the conduction system that produce arrhythmias regardless of the previous cardiovascular state. Cardiac arrhythmias are common cardiac manifestations described in COVID-19 patients [38]. A study describing clinical profile and outcomes in 138 Chinese patients with COVID-19 reported a 16.7% incidence of arrhythmia [38].

Conclusion

Until today, the origin of SARS-CoV-2 disease and its acute repercussions have been established, but the long-term sequelae in diabetic patients with cardiovascular disease are not yet well known (long COVID). Patients with COVID-19 are at increased risk of a broad range of cardiovascular disorders including cerebrovascular disease, dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure, and thromboembolic disease [39]. The risk and 1-year burden of cardiovascular disease in survivors of acute COVID-19 are substantial [40]. Most of these are lifelong conditions that will affect people for a lifetime and may impact their quality of life and other health outcomes [40].

Multiple Choice Questions

1. As a result of sedentary lifestyle, what is the expected amount of new patients who will develop type 2 diabetes?
   (a) 10 million
   (b) 9 million
   (c) 20 million
   (d) **11 million**
   (e) 15 million
2. What is the mortality rate from COVID-19 infection in patients with diabetes?
   (a) **7.8%**
   (b) 3%
   (c) 5.2%
   (d) 10%
   (e) 5.4%

3. What is the estimated percentage of patients with COVID-19 infection with severe pneumonia?
   (a) 80%
   (b) 15%
   (c) 45%
   (d) 100%
   (e) **5%**
4. What is the cardioprotective action attributed to SGLT2 inhibitors in patients with diabetes and heart failure?
   (a) Natriuretic effect
   (b) Low glycemic action
   (c) **Promote ketogenesis**
   (d) Lactic acidosis
   (e) Insulin sensibility
5. In severe COVID-19 infection, which classes of glucose-lowering drugs are recommended to avoid?
   (a) SGLT2 inhibitors and metformin
   (b) Insulin and SGLT2
   (c) DPP-4 inhibitors
   (d) Sulfonylureas
   (e) All are secure
6. What is the SGLT2 inhibitor that demonstrated a significant reduction in major adverse cardiovascular events and death from cardiovascular causes?
   (a) **Dapagliflozin**
   (b) Empagliflozin
   (c) Canagliflozin
   (d) Ertugliflozin
   (e) Phlorizin
7. What comorbidity is not associated with a higher prevalence of diabetes?
   (a) Parasitic
   (b) Bacterial
   (c) Fungicidal
   (d) **Viral**
   (e) Oncologic
8. In patients with CVD, the increase of which receptor is associated with a higher risk of cardiovascular complications?
   (a) CXCR4
   (b) GM2
   (c) **ACE2**
   (d) VLDLR
   (e) HLA-1
9. What is the percentage of athletes diagnosed with clinical and subclinical myocarditis after COVID-19 infection?
   (a) 0.31%
   (b) **2.3%**
   (c) 10%
   (d) 80%
   (e) 9.7%
10. What is the most prevalent comorbidity in patients with COVID-19 infection?
    (a) Diabetes mellitus
    (b) **Hypertension**
    (c) Chronic kidney disease
    (d) Parkinson's disease
    (e) Obesity

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Part IX

Chronic Complications

Biochemical Mechanisms of Vascular Complications in Diabetes

49

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Objectives

- To analyze the biochemical and molecular mechanism of vascular diabetic complications
- To analyze the role of metabolic alterations induced by hyperglycemia in diabetic complications (altered glycolysis, diacylglycerol production, protein kinase C activation, activation of polyol and hexosamine pathways, and glycation)
- To analyze the role of oxidative stress in diabetic complications, considering reactive oxygen species production and the biochemical, metabolic, and morphological alteration induced by them
- To analyze the role of inflammation during diabetes and its participation in vascular diabetic complications
- To analyze the integrative hypothesis that explains the rise and progression of vascular diabetic complications

Diabetes and Vascular Complications

Diabetes mellitus (DM) is a heterogeneous pandemic metabolic disorder characterized by a chronically elevated blood glucose concentration (hyperglycemia) due to resistance to insulin action, defective insulin secretion, or both (insulin dysfunction). This disease affects approximately 9% of the worldwide adult population. Type 2 diabetes is diagnosed often late when already 40% of diabetics show complications. Vascular complications of diabetes are frequently responsible for morbidity and mortality in diabetic patients [1, 2].

Hyperglycemia or chronic elevation of blood glucose has been considered as the major inductor of vascular diabetic complications [1]. Persistent exposure of tissues to high concentrations of glucose can lead to damage (glucotoxicity) of endothelium and small blood vessels (microvasculature) followed by alterations of tissues and organs, including kidney (nephropathy), eyes (retinopathy), and nerves and central nervous system (peripheral and autonomic neuropathy), which are known as microvascular complications of diabetes [3, 4]. Additionally, hyperglycemia leads to damage of big blood vessels and heart or macrovascular complications, which are associated with cardiovascular diseases such as accelerated atherosclerosis, cardiomyopathy, myocardial infarction, stroke, and peripheral arterial disease [5]. There is a growing recognition that cognitive dysfunction, encephalopathy, osteopathy, liver disease, and cancer are emerging complications of diabetes.

Besides hyperglycemia, other factors are involved in the development and progression of vascular complications such as dyslipidemia and accumulation of lipid metabolites (lipotoxicity) [6], chronic inflammation, oxidative stress, hormone and cytokine levels, hypertension, and nitric oxide (NO) deficiency.

Several mechanisms involved in the pathogenesis of diabetic complications induced by hyperglycemia have been proposed; all of them consider how the high concentration of glucose is metabolized by different pathways and conduced to the accumulation of metabolites or activation of signaling molecules that induce damage of endothelium, vascular vessels, and other tissues, causing morphological and physiological impairment of several organs. The proposed mechanism includes (Fig. 49.1):

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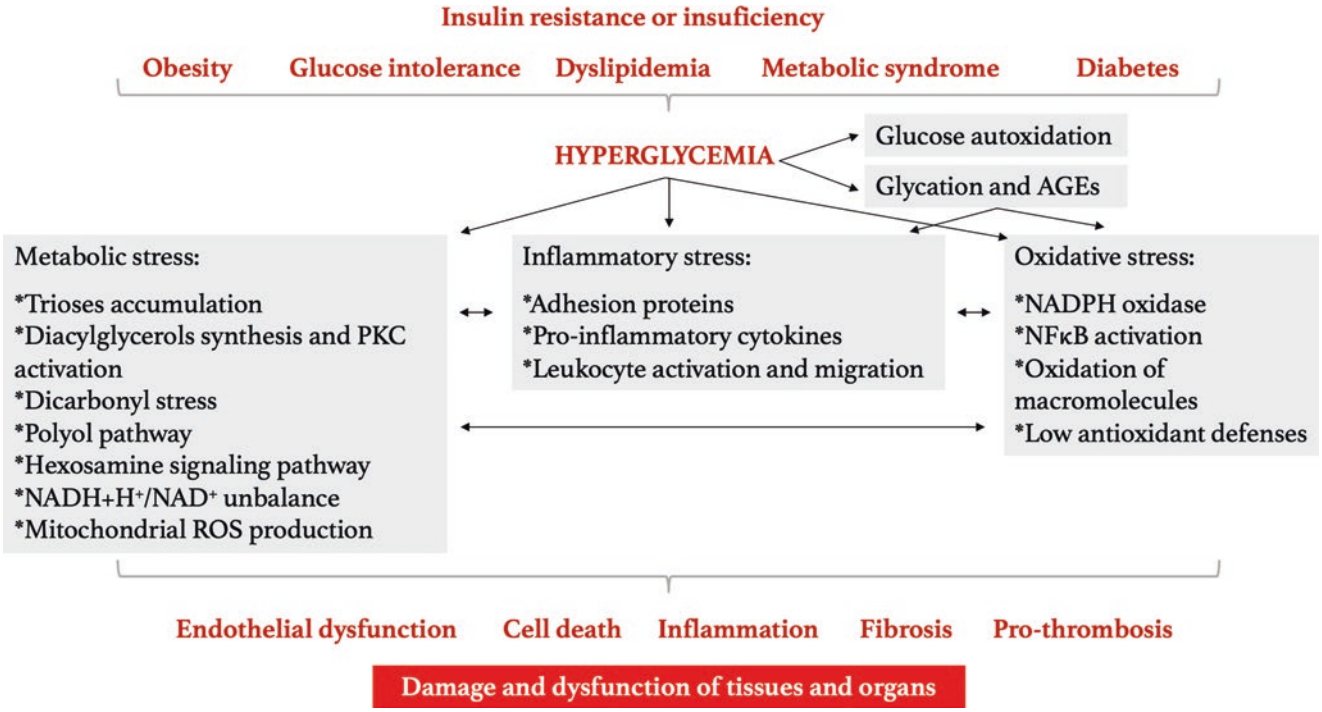

Fig. 49.1 Pathophysiological mechanisms of diabetic complications. Several chronic metabolic conditions lead to chronic or postprandial hyperglycemia, which induces metabolic, inflammatory, and oxidative stress, causing tissue and organ alterations characteristics of vascular diabetic complications. NFκB, transcription factor nuclear factor κB

1. Metabolic stress, caused by the increased flux of glucose in several metabolic pathways (Fig. 49.2), including [7]):
   (a) Glycolysis, accumulation of trioses, and generation of methylglyoxal. Trioses lead to increased formation of diacylglycerol and methylglyoxal, which are associated with the activation of protein kinase C (PKC) and intracellular glycation, respectively.
   (b) The polyol pathway and accumulation of sorbitol [7, 8].
   (c) The hexosamine signaling pathway [9].
   (d) Nonenzymatic glycation with increased formation of advanced glycation end products (AGEs) and the activation of its receptor (RAGE) [10].
2. Oxidative/reductive stress. The accumulation of reactive oxygen species (ROS) is dependent on different processes during hyperglycemia. ROS are extracellularly produced by glucose autoxidation and as a side product of glycation. Intracellularly, oxidative stress is promoted by the generation of ROS by a variety of sources such as mitochondrial electron transport chain, NADPH oxidase, xanthine oxidase, and uncoupled eNOS. An interesting point of view is that diabetic complications are majorly generated by oxidative stress driven by the NADH/NAD^+ redox imbalance (reductive stress) and mitochondrial dysfunction [4].
3. Inflammatory stress. Inflammation is a common pathophysiological mechanism in many diseases, including diabetes mellitus, where several pro-inflammatory mediators are upregulated and contribute to vascular complications.

Although multiple processes contribute to vascular complications, several researchers have treated to find one mechanism that drives the other mechanisms that conduce to the vascular complications. Three major unifying hypotheses have been proposed. The more accepted hypothesis proposes that the oxidative stress induced by hyperglycemia could be a unifying and common mechanism involved in the activation of the other mechanisms; initially, the production of ROS by the mitochondria was considered as the driver of vascular complications [9]; for example, the production of O^{2-} by the mitochondria mediates the high glucose-induced increased flux in the hexosamine pathway in bovine aorta endothelial cells [9, 11]. A second hypothesis considers the dicarbonyl stress as the key to diabetic complications [12, 13]. A third hypothesis suggests that the unifying mechanism is the polyol pathway [13, 14]. The real situation of the development of vascular complications in diabetic patients is complex. Antioxidants and pharmacological agents that inhibit these pathways have shown limited clinical success

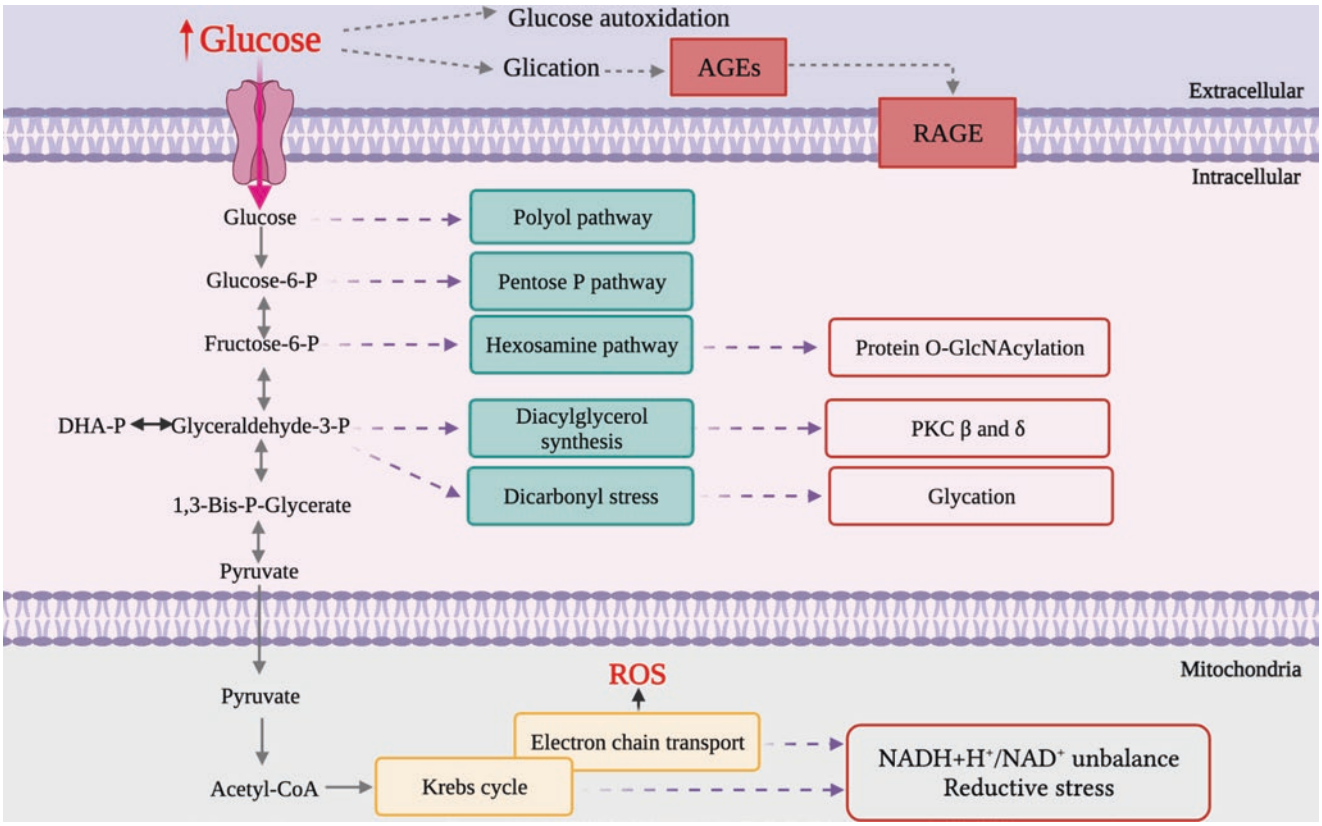

Fig. 49.2 Hyperglycemia and glucose metabolism by multiple pathways. In hyperglycemic conditions, there is an overflow of glucose uptake and metabolism in non-insulin-dependent cells, The overflow of glucose induces an NADH + H^+/NAD^+ imbalance and ROS production in the mitochondria, which lead to inhibition of glyceraldehyde-3-phosphate dehydrogenase and triose accumulation [dihydroxyacetone-phosphate (DHA-P) and glyceraldehyde-3-phosphate], leading to the activation of several pathways of glucose or glucose metabolites' disposal and associated with the induction of vascular complications. P, phosphate; RAGE, receptor for AGEs; *O*-GlcNAcylation, *O*-linked glycosylation with β, N-acetylglucosamine; PKC, protein kinase C

against nephropathy or retinopathy in diabetics. On the other hand, a proteomic analysis in long-duration type 1 diabetes mellitus patients (already of 50 years) found high levels of enzymes or the polyol pathway and electronic transfer chain in glomeruli of patients without nephropathy compared with glomeruli of patients with nephropathy [15, 16]; in this case also the enzymes of methylglyoxal depuration and the antioxidant enzyme superoxide dismutase were upregulated, and in some conditions, polyol pathway protects against inflammatory stress [15].

The central role of mitochondrial dysfunction as the initial driver of diabetic complications has been questioned [17, 18]. Some data indicate that reduced mitochondrial activity could be the basis of the progression of diabetic complications mediated by increased inflammation and pro-fibrotic factors [17]. However, the induction of inflammation by high glucose-induced oxidative stress in human vascular cells requires being primed with an inflammatory stimulus such as TNFα or IL-1β (inflammatory preconditioning), and it has been proposed that background of the inflammatory condition is necessary for the deleterious action of excessive glucose environment [19]. The inflammatory preconditioning stimulus promotes the ROS production inducing the overexpression of an important emergent source of O^{2-}, the NADPH oxidase, an enzyme that requires the coenzyme NADPH (reduced nicotinamide adenine dinucleotide phosphate), which also induces the expression of the major supply of this reduced coenzyme, glucose 6-phosphate dehydrogenase, increasing the flux of glucose in the pentose phosphate pathway [19]. Although mitochondria and NADPH oxidase have been considered the major sources of ROS during diabetes, several other ROS production pathways may be activated by hyperglycemia and glucose metabolites. These include glucose autoxidation, glycation, uncoupled endothelial nitric oxide synthase (NOS), xanthine oxidase, endoplasmic reticulum stress, cyclooxygenases, etc., and more studies are required to establish their role in diabetes pathogenesis [18].

Metabolic Stress

The mechanisms of glucose metabolism involved in diabetic complications include glucose autoxidation, the shunt of glucose to the polyol pathway, formation of AGEs, and elevated hexosamine pathway activity [7].

Polyol Pathway

The polyol pathway is linked with the progression of diabetic complications, especially retinopathy because of the formation of a vulnerable intermediate product during its course.

Polyol pathway is activated during hyperglycemia due to saturation of hexokinase (the enzyme that catalyzes the first step of glycolysis). This pathway is activated as blood glucose level rises and involves two enzymatic steps catalyzed by aldose reductase and sorbitol dehydrogenase, present in excess amounts in various body tissues. In the first step, glucose is converted into sorbitol, by the activity of aldose reductase 2 (ALR2), coupled to the oxidation of its cofactor NADPH. In the second step, sorbitol is further converted into fructose, by the action of sorbitol dehydrogenase, using NAD^+ as a cofactor and producing NADH.

This intracellular metabolic process results in the accumulation of sorbitol as an intermediate product because the cellular membranes are impermeable to sorbitol and prevent its efflux. Intracellular accumulation of sorbitol induces osmotic imbalance, water intake, and cellular death. Sorbitol is usually accumulated in the lens, retina, and kidney. The exact mechanism of sorbitol-induced cell death is unkwon but accounts for extensive cellular damage, leading to the progression of diabetic retinopathy, and contributes to nephropathy [7, 8]. The activation of ALR2 also leads to the overconsumption of NADPH, reducing its availability for glutathione reductase, the enzyme that restores reduced glutathione (GSH), the principal intracellular antioxidant, promoting oxidative stress [8].

Although the quantity of sorbitol remains high, sorbitol is converted into fructose in the second step of the reaction, and fructose also is overproduced due to 30% of blood glucose is consumed by the polyol pathway in diabetes. Fructose and some of its derivatives (3-deoxyglucose and fructose-3-phosphate) can glycate proteins altering their function, and in the liver, kidney, and intestine, fructose is phosphorylated to fructose-1-phosphate (F1P) by fructokinase. F1P is metabolized to dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3-phosphate (G3P), which enter the glycolytic/gluconeogenic metabolite pools; these reactions depend on the fructose concentration because it lacks regulatory control, and acetyl-CoA is overproduced, leading to its overflow through the tricarboxylic acid cycle and increased reductive stress. The overproduction of acetyl-CoA contributes to the development of liver steatosis and non-alcoholic fatty liver disease (NAFLD) and protein functional impairment because of their increased acetylation. In addition, the NADH produced during the second reaction contributes to the reductive stress and conduces to the production of more O^{2-} in the mitochondria [7].

An increase in the activity of the polyol pathway in tissues like the retina, kidney, peripheral nerves, and blood vessels occurs in diabetes because in these tissues, insulin is not required for glucose uptake. The role of the polyol pathway in diabetic retinopathy is supported because increased polyol pathway activity is observed in the retina from animal models of diabetic retinopathy and diabetic human donors with retinopathy [20]. Also, the C allele of the polymorphism at position −106 in the promoter of the *ALR2* gene *has been* associated with diabetic retinopathy [21]. However, the clinical use of an inhibitor of aldose reductase (epalrestat, sorbinil, tolrestat, fidarestat, etc.) is limited because some inhibitors fail to produce significant protection against vascular complications or present cytotoxicity [8]. The cytotoxicity is because these inhibitors frequently also inhibit ALD1, another isoenzyme of aldose reductase, which is involved in the detoxification of aldehydes 3-deoxyglucosone, hydroxynonenal, and methylglyoxal. The accumulation of these aldehydes causes cytotoxicity. Of aldose reductase inhibitors, only epalrestat is used against diabetic neuropathy in Japan, China, and India. However for safety concerns, epalrestat has not been approved yet in some countries and was withdrawn from the market of a few countries [8]. Considering that in some conditions aldose reductase has a protective role against inflammatory and oxidative stress, the use of their inhibitors for the treatment of vascular complications must be carefully evaluated [16].

Hexosamine Biosynthesis Pathway and *O*-GlcNAcylation of Proteins (Fig. 49.3)

Increased flux of glucose into the hexosamine signaling pathway has been implicated in diabetic vascular complications and is induced by hyperglycemia. In this case, glucose 6-phosphate is isomerized to fructose 6-phosphate in glycolysis, and the overproduction of fructose 6-phosphate under hyperglycemic conditions is canalized to this pathway as an alternative to glycolysis [22]. Glucosamine 6-phosphate is produced by the transference of an amino group of glutamine to fructose 6-phosphate catalyzed by the rate-limiting enzyme glutamine-fructose-6-phosphate amidotransferase (GFAT). Finally, in the hexosamine pathway, uridine nucleoside diphosphate-N-acetylglucosamine (UDP-GlcNAc) is formed by sequential enzymatic steps. UDP-GlcNAc is a donor molecule that leads

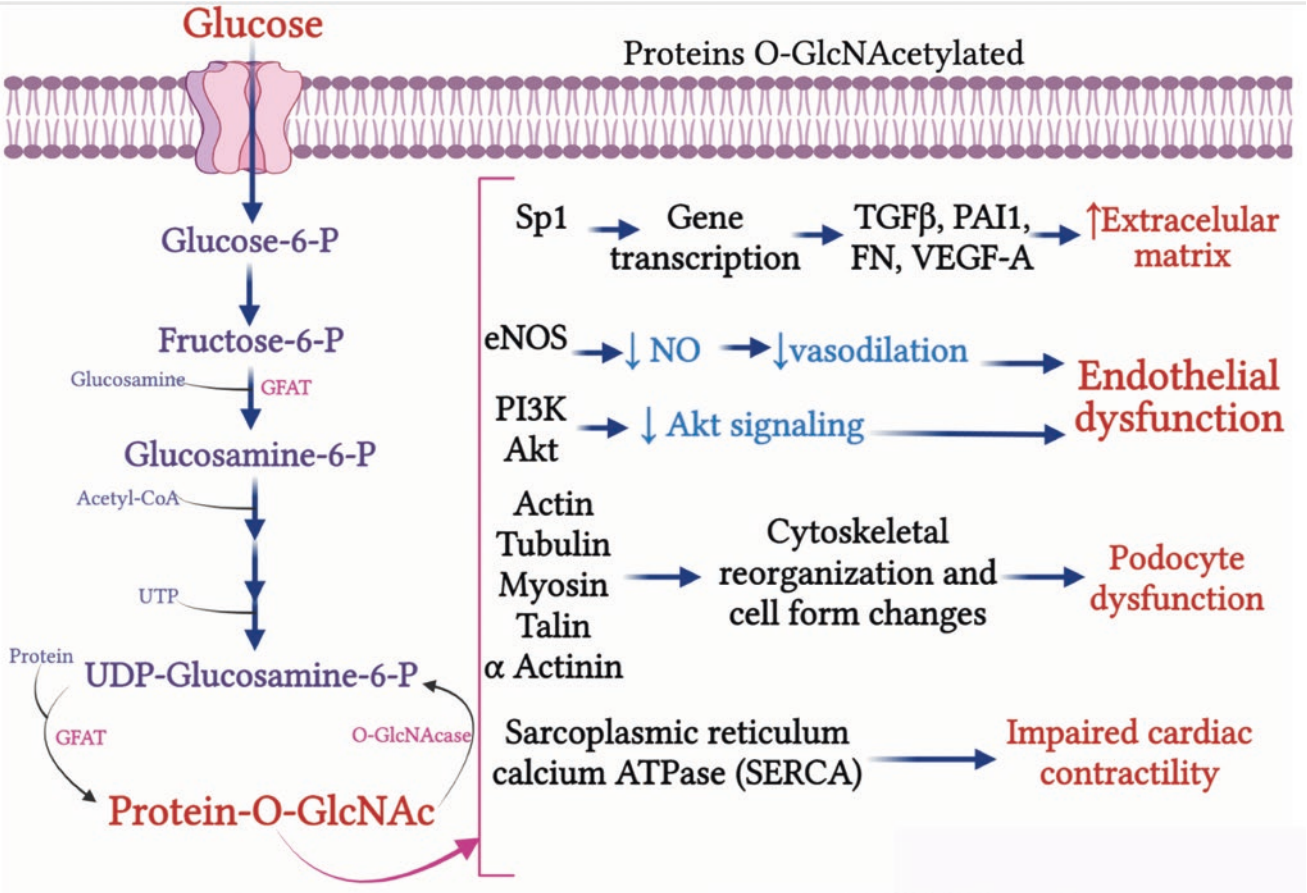

Fig. 49.3 O-GlcNAcetylated proteins and their contribution to vascular complications. The O-GlcNAcetylation of several proteins contributes to different alterations that conduce to vascular complications of diabetes. GFAT, glutamine-fructose-6-phosphate amidotransferase; Sp1, specificity protein 1; FN, fibronectin; NO, nitric oxide; P, phosphate

to *O*-linked glycosylation with the hexosamine-derived β, N-acetylglucosamine (*O*-GlcNAcylation) by the enzyme *O*-GlcNAc transferase (OGT) to serine and threonine residues on target proteins. Conversely, GlcNAc is removed from proteins by GlcNAcase (OGA) (Fig. 49.3).

O-linked N-acetyl glucosamine (O-GlcNAc) is highly increased in cells and tissues of diabetic animals and patients and serves as a nutrient/stress sensor since the synthesis of its donor UDP-GlcNAc depends on changes in the glucose, amino acid, fatty acid, and nucleotide concentrations. Activation of hexosamine signaling pathway mediates several deleterious effects of hyperglycemia through the *O*-GlcNAcylation of proteins modifying their activity. Acutely *O*-GlcNAc probably plays a protective function against stress-induced inflammation. However, persistent *O*-GlcNAcylation of proteins induced by hyperglycemia is involved in changes of gene transcription, cell signaling, vasodilatation, cytoskeletal organization, and apoptosis of endothelial cells and neurons associated with vascular complications [23]. For example, *O*-GlcNAcylation of endothelial nitric oxide synthase (eNOS), the protein kinase Akt, and the transcription factor specificity protein 1 (Sp1) lead to decreased NO production, attenuated endothelial migration, and altered gene expression, respectively.

The modification of gene expression by hyperglycemia is associated with increased *O*-GlcNAcylation and decreased serine/threonine phosphorylation of the transcription factor Sp1 (Fig. 49.3). Sp1 induces the expression of transforming growth factor-β (TGFβ), plasminogen activator inhibitor 1 (PAI-1), and vascular endothelial growth factor A (VEGF-A) [9, 24]. The proliferation of vascular cells is triggered by VEGF-A during diabetic retinopathy. These changes in gene expression could be prevented by the inhibition of the rate-limiting enzyme GFAT or inhibitors of OGT. On the other hand, inhibition or overexpression of the enzyme that degrades N-acetyl glucosamine, O-GlcNAcase (OGA), increases the expression of VEGF-A in cultured retinal cells [24] or reverses the coronary endothelial cell dysfunction in streptozotocin-induced diabetic mice [25].

Few studies link O-GlcNAc to vasculature dysfunction in human T2DM. Arterial or venous endothelial cells obtained from patients with T2DM are characterized by endothelial

insulin resistance and lower NO production. Endothelial O-GlcNAc levels are higher in T2DM patients than in non-diabetic controls and are directly correlated with serum fasting blood glucose and glycated hemoglobin A1c (HbA1c) levels. When endothelial cells from patients with T2DM are cultured in normal glucose conditions (24 h at 5 mmol/L), O-GlcNAc levels are lowered and insulin-mediated activation of endothelial nitric oxide synthase is restored. Moreover, the inhibition of the removal of O-GlcNAc from proteins using thiamet G, an O-GlcNAcase inhibitor, in endothelial cells increases O-GlcNAc levels and blunted the improvement of insulin-mediated endothelial nitric oxide synthase phosphorylation by glucose normalization. These data indicate that O-GlcNAc modification is implicated in the glucose-induced impairment of endothelial nitric oxide synthase activation in endothelial cells from patients with T2DM. O-GlcNAc protein modification may be used in the diagnosis and as a treatment target for vascular dysfunction in T2DM [26].

Synthesis of Diacylglycerols and Protein Kinase C Activation

In hyperglycemic conditions, triose phosphates and glycerol-phosphate are accumulated, resulting from the inhibition of the enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH) by the NADH overproduction and oxidative stress. Both triose phosphate and fructose (end products of the polyol pathway) lead to the formation of methylglyoxal and diacylglycerol (DAG). DAG is located in the cell membrane and activates classical isoforms of PKC (PKCα, PKCβ, and PKCδ), which induce several cell responses and lead to the production of reactive oxygen species via upregulating the expression of NADPH oxidases. PKC is also activated by ROS.

Activated PKC functions through the phosphorylation of Ser and Thr residues in its target proteins and regulates various processes related to diabetic vascular complications such as NO production, vascular permeability, angiogenesis, apoptosis, endothelial dysfunction, and basement membrane thickening. PKCδ can accelerate apoptosis of pericytes, capillary cells, resulting in the degeneration of capillaries during retinopathy. This kinase also induces the apoptosis of podocytes in culture and endothelial dysfunction in renal glomeruli of diabetic rats and mice, in a mechanism mediated by the p38 MAPK and Src homology-2 domain-containing phosphatase-1 (SHP-1) [27, 28]. The relevance of PKCδ in diabetic complications is supported by the fact that the diabetic PKCδ-knockout (Prkcd(−/−) mice present decreased expressions of TGFβ, VEGF, and extracellular matrix and less albuminuria than diabetic PKCδ wild-type mice [28]. Poor wound healing in diabetic patients has been attributed to activation of PKCδ in fibroblasts, and pharmacologic inhibition and knockdown of PKCδ in diabetic fibroblasts improve wound healing when fibroblasts are implanted in nude mice [29].

Activation of the other isoform PKCβ in endothelial cells induces endothelin 1 expression and enhances VEGF action, increasing vascular endothelial permeability and endothelial dysfunction [27]. Clinical trials using a selective inhibitor of PKCβ ruboxistaurin that ameliorated retinal hemodynamic abnormalities in diabetic patients have not yielded very promising results; further additional clinical trials are needed using inhibitors of the PKCδ isoform.

Glycation and Advanced Glycation End Products

Glycation is defined as the no enzymatic reaction between glucose and reducing sugars with amino groups of proteins, lipids, or nucleic acids. This reaction is promoted under hyperglycemia, oxidative stress, or aging and alters the structure and function of macromolecules.

Glycation begins with the nonenzymatic reaction between aldehyde groups of glucose with amino groups in macromolecules forming first the reversible Schiff base adducts, which are rearranged to more stable, covalently bound Amadori products. Over days to weeks, early glycation products undergo further reactions such as rearrangements and dehydration to become irreversibly cross-linked, fluorescent derivatives called advanced glycation end products (AGEs), such as carboxymethyl lysine (CML), carboxyethyl lysine, pentosidine, or pyrraline derived from proteins, and N(2)-carboxyethyl-2′-deoxyguanosine (CEdG) derived from DNA [10]. AGEs are also generated in highly heated and processed foods and can be obtained from the diet.

AGEs are accumulated in several tissues of diabetic patients or experimental animals including microvasculature, aorta, retina, kidney, pancreas, colon, or skin [30, 31]. The plasma concentration of HbA1c, the Amadori adduct of the N-terminal valine of the hemoglobin β-chain, is used as a long-term biomarker of glycemic control in clinical practice; there is a linear relationship between HbA1c and mean blood glucose; however, HbA1c reflects the average glucose over ∼120 days, the mean lifetime of the erythrocyte. Plasma, serum, and urinary levels of AGEs are correlated with the severity of complications in diabetic patients [32–34].

AGEs directly affect the function of macromolecules; for example, nucleotide AGEs are associated with DNA single-strand breaks and increased mutation frequencies. Also AGEs bind with AGE-binding receptors (RAGE). RAGE is a multi-ligand cell surface protein, expressed by endothelial cells, monocytes/macrophages, smooth muscle cells, neu-

rons, podocytes, cardiomyocytes, adipocytes, podocytes, lung epithelial cells, and some cancer cells. The binding of AGEs with RAGE leads to the generation of oxidative stress, inducing proliferative, migratory, inflammatory, thrombotic, and fibrotic reactions in a variety of cells, which leads to alterations associated with diabetic vascular complications [5, 35]. Enhanced production of O^{2-} induced by hyperglycemia in vascular endothelial cells is linked with the production of AGEs and the expression of its receptor. Also, elevated levels of AGEs induce the expression of its receptor amplifying the AGE signaling [36]. The generation of ROS induced by AGEs-RAGE interaction is primarily mediated by the activation of NADPH oxidase, and further, the ROS production can be amplified in the mitochondria.

The fibrotic action of AGEs in renal and vascular cells is mediated by TGFβ-dependent and TGFβ-independent mechanisms, both are dependent on AGEs-RAGE interaction; in the first case, the expression of TGFβ is induced and TGFβ leads to the activation of the transcription factors Smads, which induce expression of pro-fibrotic proteins (ECM proteins, TGFβ receptor 1 or TGFβR1, connective tissue growth factor or CTGF, and PAI-1). In the second case, Smads are activated secondary to the activation of the ERK/p38 mitogen-activated protein kinases (MAPK) signaling pathway [37, 38].

The activation of RAGE also has been associated with sustained activation of the transcription factor NFκB (nuclear factor kappa B), resulting initially from the degradation of its inhibitor IkB and the translocation of NFκB to the nucleus and chronically by NFκB increased de novo synthesis [39].

The signaling mechanism induced by RAGE activation begins with the interaction of its highly charged cytoplasmic domain with the formin homology domain of diaphanous 1 (DAPH1). DAPH1 is required for RAGE signaling, which is blocked by the knockdown of the D*iaph1* gene. DAPH1 is a cytoplasmic actin-binding protein and after the activation of RAGE signaling leads to the activation of several effectors such as Rho GTPases (Rac 1 Cdc 42, and RHOA) and others. Rho GTPases are associated with actin cytoskeleton dynamics and the induction of cell migration in cancer and smooth muscle cells [5, 40]. Rac 1 also conducts the activation of NADPH oxidase and oxidative stress.

Recently, RAGE-DIAPH1 interaction has been considered therapeutic targets, and small molecule inhibitors of this interaction suppress the induction of migration and production of inflammatory cytokines by RAGE ligands in cultured smooth muscle cells and TH1 macrophage-like cells [41].

In addition, there are two forms of soluble RAGE: one derived from proteolytic processing of the membrane receptor or soluble RAGE (sRAGE) and another derived by alternative splicing or endogenous soluble RAGE (esRAGE).

Nuclear Factor Kappa B (NFκB)

The NFκB family of transcription factors regulates the expression of proteins involved in cell proliferation and survival, inflammation, and immune and oxidative stress responses. In physiological conditions, NFκB is induced in an adaptive response to maintain homeostasis; however, the sustained activation of NFκB is thought to have a central role in the pathogenesis of several chronic diseases including diabetes and their complications. NFκB induces the expression of several genes as a response to stressful stimuli like oxidative stress, hyperglycemia, and inflammation. The activation of NFκB is induced by a variety of stimuli including free reactive oxygen species, AGEs, pro-inflammatory cytokines, oxidized low-density lipoproteins, free fatty acids, and bacterial and viral antigens. When NFκB is not activated, it is located in the cytoplasm, forming a complex with its inhibitor IκB (inhibitor of NFκB); after the activation of the upstream signal, the inhibitor is phosphorylated by the IκB kinase (IKK) and degraded through the ubiquitin system. As a consequence, NFκB is released and translocated into the nucleus, where it activates the expression of target genes. The principal regulatory step in the activation of NFκB is the phosphorylation and activation of IKK. NFκB regulates the expression of pro-inflammatory proteins, including adhesion molecules in endothelial cells such as intracellular cell adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM), cytokines (TNFα, IL-1β), and chemokines. NFκB signaling is a potential target for therapeutic intervention, and several inhibitors of NFκB activation and signaling have been developed.

Dicarbonyl Stress, Methylglyoxal, and Endogenous Glycation

Levels of reactive aldehydes like methylglyoxal, glyoxal, and 3-deoxyglucosone are elevated in diabetes mellitus. Methylglyoxal has been related to diabetic complications for its ability to induce insulin and vascular dysfunction and to cause neuropathic pain because its generation is induced by chronic hyperglycemia. Also, its plasma concentration is elevated in diabetic patients [42]. Methylglyoxal is an α-dicarbonyl and might be the most important reactive aldehyde in diabetes and its complications. Methylglyoxal is formed as a by-product of glycolysis by fragmentation of triose phosphates accumulated in glycolysis and also is derived from the catabolism of threonine and ketone bodies, lipid peroxidation, and degradation of glycated macromolecules.

The accumulation of methylglyoxal and similar compounds also depends on their lower detoxification by the glyoxalase system. This system catalyzes the detoxification of

reactive dicarbonyls in the cytoplasm, providing the principal defense against dicarbonyl glycation. The efficiency of this system is reduced by chronic hyperglycemia, because the rate-limiting enzyme, glyoxalase 1 (Glo1), is down-regulated in a high-glucose environment [12]. Glyoxalase 1 down-regulation is induced by RAGE signaling and the pro-inflammatory activation of NFκB [12]; in this case, the action of NFκB is mediated by the non-transcriptional inhibition of the antioxidant response [43].

Methylglyoxal through the glycation reaction modifies proteins and nucleic acid, being the precursor of endogenous AGEs, including arginine-derived hydroimidazolones and deoxyguanosine-derived imidazopurinones, and also induces apoptosis in vascular cells fomenting endothelial dysfunction and the progression of vascular complications including atherosclerosis [44].

Recently, it was described that the plasma concentrations of methylglyoxal and other oxo-aldehydes (glyoxal and 3-deoxyglucosone) are enhanced after carbohydrate load in type 2 diabetes, which was associated with increased risk of diabetic complications induced by elevations of postprandial glycemia [45].

NADH Overproduction or Reductive Stress

During hyperglycemia, the uptake of glucose increases in non-insulin-dependent tissues, leading to a high level of glucose metabolism as glucose entry into the cells is not limited by insulin deficiency. The increased flux of metabolites in glycolysis and the citric acid cycle in the mitochondria leads to high production of NADH, a coenzyme that receives electrons derived from oxidative degradation of glucose and provides electrons to the electron transport chain, leading to the formation of ATP and oxygen reduction. The NADH/NAD^+ imbalance is accentuated also by the production of NADH in the activated polyol pathway and by the consumption of NAD^+ by the nuclear enzyme poly ADP-ribose polymerase 1 (PARP-1) that uses NAD^+ as substrate.

The redox imbalance of NADH/NAD^+ causes initially reductive stress or pseudohypoxic stress that leads to oxidative stress. The excess of NADH promotes oxidative stress because the overflow of electrons in the electron transfer chain leads to leaking of electrons and partial reduction of oxygen with increased production of O^{2-} and other reactive oxygen species [3, 4]. Accordingly, oxidative damage triggered by redox imbalance might be a major factor contributing to the development of diabetic complications, and the prevention of NADH/NAD^+ redox imbalance could provide further insights for the design of novel antidiabetic strategies.

Oxidative Stress

As we discussed before, the electron overflow in the electron transport chain in non-insulin-dependent tissue under a hyperglycemic microenvironment leads to electron leaking and O^{2-} production in the mitochondria [3, 4]. The excessive production of ROS during diabetes overwhelms endogenous antioxidant defense mechanisms causing an imbalance in the production of ROS and nonenzymatic and enzymatic antioxidant mechanisms in the body, which ultimately leads to oxidative stress.

Additionally, in the production of ROS in the mitochondria, other sources of ROS have been described in diabetic condition, including NADPH oxidase, xanthine oxidase, and uncoupled eNOS, with NADPH oxidases being of special importance. There are several isoforms of O^{2-}-producing NADPH oxidase in the endothelium, smooth muscle cells, and adventitia of the vascular wall [46]. The activation and upregulation of NADPH oxidases are induced by PKCβ and PKCδ, AGEs-RAGE interaction, and inflammatory cytokines (TNFα), all of them considered as promoters of diabetic complications. NADPH oxidase is a multiprotein complex associated with the membrane.

Enhanced ROS levels induce oxidative modification of macromolecules, including lipids in the membranes (lipid peroxidation), enzymes, and nucleic acids altering their functions and cell integrity. As products of lipid peroxidation, malondialdehyde and 4-hydroxy 2-nonenals (4-HNE) are formed; when ROS react with DNA, 8-dihydro-8-oxo-2′-deoxyguanosine (8-OxodG) is produced and is removed during oxidized DNA repair and excreted in the urine. These compounds have been used as markers of oxidative stress. The highly reactive 4-HNE form covalent adducts with nucleophilic functional groups in proteins, nucleic acids, and membrane altering their functions and causing cytotoxicity or modulating a variety of signaling processes. At physiological or low concentration, 4-HNE induces cell survival or antioxidant response, becoming cytostatic and cytotoxic at higher levels. The signaling action of 4-HNE is mediated by transcription factors sensible to stress, including NFκB, nuclear factor erythroid 2-related factor 2 (Nrf2), and activating protein-1 (AP-1) [47].

Oxidative modifications of proteins (carbonylation, intermolecular dityrosine cross-linking, thiol oxidation, etc.) lead to the formation of advanced oxidized protein products (AOPPs), which induce pro-inflammatory and pro-fibrotic processes and cell death associated with progression of nephropathy and atherosclerosis. AOPPs induce inflammation by the activation of neutrophils and monocytes through NFκB activation mediated by NADPH oxidase [48]. Some actions of AOPPs are induced by their binding to RAGE in endothelial cells and podocytes [49].

DNA damage caused by oxidative stress leads to the overactivation of PARP-1. PARP-1 transfers ADP-ribose from NAD^+, leading to the formation of poly ADP-ribose (PAR) and nicotinamide; the decrease in NAD^+ and ATP levels causes energy failure and cell necrosis [3, 4]. The mechanism of cell death induced by PARP has been recently elucidated; PARP induces the release of apoptosis-inducing factor (AIF) from the mitochondria, and AIF binds to macrophage inhibitory factor (MIF), a protein with a recently discovered activity of nuclease; this complex is translocated to the nucleus, resulting in DNA fragmentation and cell death, through a caspase-independent type of cell death, designated parthanatos [50].

The activation of PARP also conduces to an inflammatory condition, since PARP-1 promotes the expression of pro-inflammatory factors, including TNFα and IL-1β, and the inhibition of PARP is a promising strategy for the prevention and treatment of diabetic complications. The inhibition of PARP ameliorates cardiovascular complications and nephropathy in an animal model of type 2 diabetes, preventing oxidative stress, inflammation, and renal fibrosis [51, 52]. It also attenuates the development of retinopathy in streptozotocin-induced diabetic rats [53] and prevents the apoptosis of cultured cardiomyocytes under high glucose concentration [54].

Although supplementation with antioxidants has been considered in the treatment of diabetic complications, interventional trials with supplemented antioxidants have failed to show significant beneficial effects. Conversely, the use of natural foods shows promising results, and the employment of a balanced "Mediterranean diet" helps in the control of free radical production and increases intracellular antioxidant defenses [55]. Early intensive glucose control is still the best strategy to avoid oxidative stress and its associated diabetic complications.

Altered Lipid Metabolism, Dyslipidemia, and Accumulation of Cytotoxic Lipids

Diabetic dyslipidemia leads to changes in systemic and local lipid metabolism that drive the pro-inflammatory and pro-apoptotic cellular changes typical of diabetic complications. Abnormalities in metabolism, accumulation, and plasma profile of lipids have been associated with insulin resistance and vascular complications [6], and several studies support the potential benefits of lipid-lowering diets and drugs, such as Mediterranean diet, omega-3 fatty acids, fibrates, and statins, for the prevention and treatment of vascular complications. A positive association between high levels of total cholesterol, low-density lipoproteins (LDL), and LDL/high-density lipoproteins (HDL) ratio and vascular complications are well established. Recently the profile of plasma ceramides has been proposed as risk factors and prognosis indicators of predisposition and progression diabetes mellitus and its complications. Thus, the circulating levels of ceramide containing C16, C18, or C24 acyl chains display a superior predictive value for future adverse cardiovascular events (myocardial infarction and stroke) and plaque instability than LDL cholesterol.

Lipids and their transporting lipoproteins like LDL and HDL are glycated and/or oxidized during chronic hyperglycemia and oxidative stress. These modified lipoproteins promoted endothelial dysfunction and vascular injury due to the activation of RAGE receptors [56] and have cytotoxic, pro-inflammatory, and pro-atherogenic effects; for example, they activate the release of pro-inflammatory cytokines by retinal glial Muller cells and are cytotoxic to retinal capillary pericytes and retinal pigment epithelial cells promoting diabetic retinopathy.

Dyslipidemia and increased levels of plasmatic free fatty acids (FFA) lead to lipid peroxidation and the increased uptake of FFA in the cells. Intracellularly fatty acids are oxidized in the mitochondria producing acetyl-CoA or are used in the synthesis of di- and triacylglycerols, glycerophospholipids, and ceramide, the precursor of sphingolipids. Diacylglycerol can activate PKC, triacylglycerols can be accumulated in hepatocytes or cardiomyocytes causing steatosis and functional alterations, and ceramides have been associated with diabetic complications. The spectrum of sphingolipid actions in diabetes shifts from protective very-long chain (VLC) ceramides ($C \geq 26$) to pro-inflammatory and pro-apoptotic short-chain (SC) ceramides ($C \leq 24$). SC ceramides are mainly produced from sphingomyelins by acid sphingomyelinase (ASM), whose level increases in tissues and blood during diabetes.

SC ceramides promote intrinsic apoptosis by the increase of mitochondrial outer membrane permeability through the formation of protein-permeable ceramide channels that allow the release of cytochrome c in the cytoplasm. During diabetes, ceramides are accumulated and induce apoptosis in renal mesangial and tubular epithelial cells, contributing to diabetic nephropathy; also they induce apoptosis of retinal pericytes and contribute to the breakdown of the blood-retinal barriers and the development of retinopathy [6, 57].

Inflammatory Stress

Inflammation is induced by oxidative stress and diverse factors and is a common pathophysiological characteristic in many diseases, and diabetes is associated with a chronic pro-inflammatory condition, which is evidenced by increased serum levels of pro-inflammatory cytokines (TNFα) in diabetic patients and experimental animals [52]. Additionally,

the transcription factor NFκB is activated in circulating lymphocytes of type 2 diabetic patients [58] and in a variety of tissues of diabetic animals (kidney, heart) [51, 52]. NFκB is activated by oxidative stress, TNFα, or angiotensin II (Ang II) and regulates the expression of a variety of inflammatory-related genes, including pro-inflammatory cytokines like TNFα, interleukin (IL) 1β (IL-1β), IL-6, and monocyte chemoattractant protein 1 (MCP-1); additionally, it induces the expression of cyclooxygenase-2 (COX-2), the enzyme that controls the synthesis of pro-inflammatory eicosanoids.

Ang II is a key mediator of the renin-angiotensin system (RAS), whose activation is thought to be a major mechanism underlying inflammation in diabetic complications. Ang II induces the activation of NFκB and the synthesis and release of pro-inflammatory mediators, primarily cytokines TNFα, IL-1β, and IL-6. TNFα induces macrophage recruitment and synthesis and secretion of IL-6. IL-6 stimulates the production and secretion of C-reactive protein (CRP), a key risk factor for cardiovascular diseases.

TNFα induces the expression of MCP-1 and cellular adhesion molecules in the endothelium, such as intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), which leads to recruitment of leukocytes to the surface of endothelium, contributing to the endothelial dysfunction. Further leukocytes migrate across the endothelium, causing endothelial damage and inflammation in the kidney and destruction of the blood-retinal barrier, characteristics of nephropathy and retinopathy. IL-1β induces the expression of inducible nitric oxide synthase (iNOS), causing overproduction of NO, which forms peroxynitrite when it reacts with O^{2-}, amplifying the inflammatory response and producing nitrosoactive stress.

TNFα and IL-1β can induce apoptosis directly or indirectly in cardiomyocytes and neurons, contributing to cardiac dysfunction, retinopathy, and neuropathy. Additionally, TNFα is associated with cardiomyocyte hypertrophy and cardiac fibrosis, leading to heart failure.

TGFβ and Epithelial Mesenchymal Transition in Diabetic Nephropathy (Fig. 49.4)

One of the tissue changes of diabetic nephropathy is the excessive deposition of extracellular matrix (ECM) in the

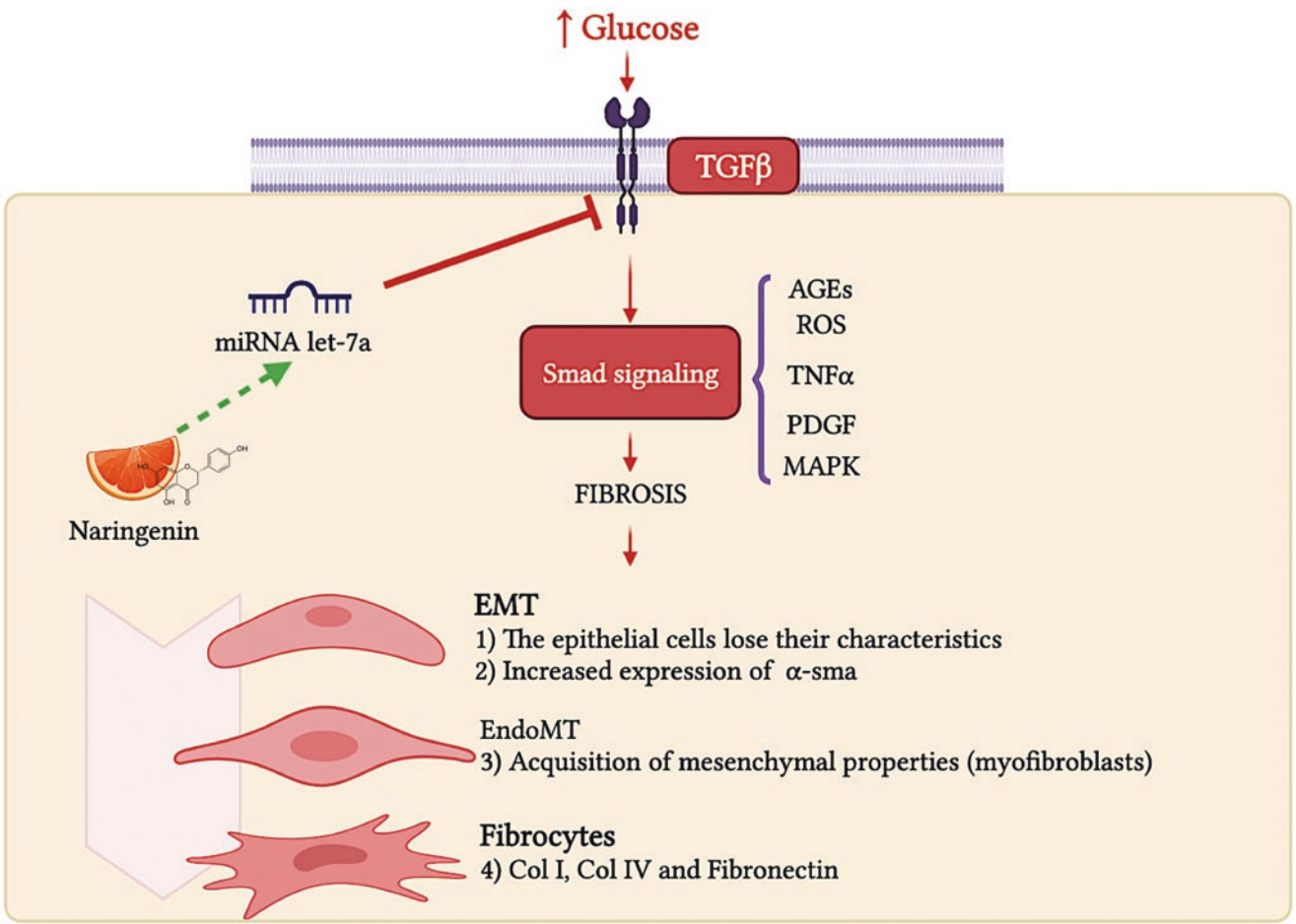

Fig. 49.4 TGFβ and epithelial mesenchymal transition in diabetic nephropathy

glomerulus and the tubular interstitium associated with the development of glomerulosclerosis and tubule interstitial fibrosis. The major source of renal ECM is myofibroblasts, whose number is increased in diabetic nephropathy. These cells are originated from different resources including activated renal fibroblasts, pericytes, epithelial-to-mesenchymal transition (EMT), endothelial-to-mesenchymal transition (EndoMT), bone marrow-derived cells, and fibrocytes [59].

EMT is one of the sources of matrix-generating fibroblast. During EMT, epithelial cells (proximal tubular cells and podocytes) lose their epithelial characteristics (down-regulation of epithelial adhesion protein, E-cadherin) and acquired mesenchymal properties originating from myofibroblasts [59, 60]. During the formation of myofibroblasts, the expression of α-smooth muscle actin (α-SMA) is induced. TGFβ is a major driver for renal fibrosis, and the inhibition of TGFβ signaling significantly reduces renal fibrosis, ameliorating kidney damage and dysfunction. TGFβ induces EMT, EndoMT, and synthesis of EMC proteins (collagen I, collagen IV, and fibronectin). The promotion of fibrosis by TGFβ is mediated by the activation of the transcription factors Smads; therefore, TGFβ/Smads signaling is considered a potential therapeutic target in the prevention and treatment of renal fibrosis [59, 61]. However, Smads signaling also can be activated for other factors, including AGEs, ROS, TNFα, platelet-derived growth factor (PDGF), MAPK, and chemokines [38, 59].

Recently, it was found that the microRNA, let-7a, negatively regulates the expression of TGFβR1, preventing the induction of fibrosis by hyperglycemia on kidney mesangial cell, and naringenin (4,5,7-trihydroxy flavanone), a flavanone compound extracted from citrus fruits, upregulates let-7a and prevents the ECM deposition in the kidney of diabetic rats [62].

Endothelial Dysfunction and Nitric Oxide Deficiency

The endothelium lines the inner surface of blood vessels and modulates vascular function and structure. It controls vascular morphology, tone, permeability, inflammation, and thrombosis by the production of a variety of mediators including vasodilators (NO and prostacyclin) and vasoconstrictors (endothelin and thromboxane). This tissue is a key in the development of diabetic complications. Endothelial dysfunction is induced in diabetes by the abnormal glucose concentration and the increase of AGEs linked with plasma lipoproteins. High glucose, the activation of RAGE by AGEs-lipoproteins, and inflammatory cytokines lead to an inflammatory reaction in the vascular wall, endothelial oxidative stress, and NO deficiency, which play a major role in inducing endothelial apoptosis. Endothelial dysfunction alters the control of vascular properties by endothelium toward reduced vasodilatation and a pro-inflammatory and pro-thrombotic state [56, 63].

Reduced vasodilatation is associated with NO deficiency or reduced availability of NO, which is induced by different factors, including reduced synthesis and the reaction of NO with O^{2-}-forming peroxynitrite ($ONOO^{-}$) in hyperglycemia and oxidative stress conditions. Although the enzyme that synthesizes NO in the endothelium, the eNOS, is upregulated by oxidative stress (hydrogen peroxide, product of the dismutation of superoxide) or PKC [64], its essential cofactor (6R-)5,6,7,8-tetrahydrobiopterin (BH4) is oxidized by peroxynitrite. When this cofactor is oxidized, the reaction of eNOS is uncoupled, and ROS are produced instead of NO, accentuating the vascular oxidative stress [63]. Inhibitors of PKC reduce eNOS expression levels in vascular endothelium. Additionally, there is a deficiency in the substrate of NOS L-arginine due to the increase of the enzyme arginase in plasma and tissues; arginase degrades L-arginine to urea and L-ornithine [65].

Since reduced bioactivity of nitric oxide (NO) is present in diabetes, some strategies are being considered to restore NO availability; one is the promotion of NO synthesis by the supplementation of L-arginine or L-citrulline; the former is the precursor of NO production by eNOS, and its plasma concentration is decreased by diabetes, whereas L-citrulline is a neutral alpha-amino acid, found in high concentrations in watermelon. L-citrulline is an inhibitor of arginase and prevents the degradation of L-arginine; also it can be recycled to L-arginine in the mitochondria by the urea cycle; therefore L-citrulline leads to increased L-arginine bioavailability. Another strategy is to supply inorganic nitrate abundant in green leaft vegetables and beetroots, which provide NO by an unconventional via.

Oral L-arginine supplementation has been inefficient to restore NO because it is removed from the intestinal tract and liver, which does not occur with L-citrulline, and its supplementation is effective at increasing blood L-arginine and endothelial NO synthesis. L-citrulline at a dose of 2000 mg/day for 1 month increased NO levels and decreased arginase levels in the plasma of T2DM patients [65]. L-citrulline can be beneficial for diabetic patients considering these data and that L-citrulline has shown an antihypertensive action in adult patients and, in preclinical assays, L-citrulline protects the endothelial function [65]. The supplements of nitrates ameliorate or prevent the risk of diabetes and its complications in animal models; nitrate is used as a precursor for NO synthesis through serial reductions of nitrate by the nitrate-nitrite-NO pathway. This pathway acts as a backup system when NOS system is compromised during diabetes and other pathological con-

ditions [66]. However, in human beings, nitrate-nitrite-NO pathway supplements have had poor results and probably required ascorbic acid complementation [67]. The protective action of NO has been attributed to the inhibition of NADPH oxidase activity mediated by the heme oxygenase-1 (HO-1)-dependent antioxidant mechanism, preventing the vascular oxidative stress and endothelial dysfunction [68].

When the endothelium is damaged, soluble forms of the adhesion proteins ICAM (sICAM-1), VCAM (sVCAM), and E-selectin are released from the endothelial surface, and its plasma concentration is evaluated as markers of endothelial cell dysfunction [56]. Plasma sICAM-1 concentration is increased in diabetic albuminuric patients before signals of nephropathy. Plasma ICAM-1 concentrations are negatively correlated with the vasodilatory function of the endothelium. Because oxidative stress contributes to endothelial dysfunction, a positive correlation was found between plasmatic concentrations of advanced oxidized protein products (AOPPs) and sICAM [69].

Anaerobic Metabolism and Neuropathic Pain

Nowadays, a link between anaerobic metabolism and neuropathic pain has been established. The pyruvate dehydrogenase kinase (PDK)-lactic acid axis is a critical link that connects metabolic reprogramming and neuropathic pain. Pyruvate dehydrogenase (PDH) catalyzes the irreversible oxidative decarboxylation of pyruvate to acetyl-CoA, and its activity is lost when is phosphorylated by PDK in anaerobic conditions. PDKs are upregulated in the tissues of patients and rodents with diabetes. A nociceptive role for lactate is recently recognized; lactate is the predominant end product of anaerobic glycolysis. Some tissues and organs like dorsal root ganglion are exposed to a low-oxygen condition (ischemia) during diabetes; in this condition, PDKs 2 and 4 are upregulated; these enzymes inactive PDH by phosphorylation; therefore pyruvate is transformed to lactate by lactate dehydrogenase, and the accumulation of lactate induces the expression of pain-related ion channels and neuroinflammation, leading to pain hypersensitivity and diabetic neuropathy. Suppression of *Pdk2 and Pdk4* expression attenuated the hyperglycemia-induced pain hypersensitivity and induced partial resistance to the diabetes-induced loss of peripheral nerve structure and function in streptozotocin-induced diabetic mice [70].

Concluding Remarks

- The pathophysiological mechanism leading to vascular diabetic complications includes the metabolic, oxidative, and inflammatory alterations induced by hyperglycemia.
- Increased metabolic flux of glucose leads to activation of polyol and hexosamine pathways and accumulation of trioses, dicarbonyl aldehydes, and diacylglycerols, together with NADH/NAD^+ redox imbalance, oxidative stress, and PKC activation.
- ROS, peroxynitrites, lipid peroxidation, and glycation cause chemical modification of macromolecules, leading to the loss of their function, nucleic acid alterations, and apoptosis.
- The interaction of AGEs with its receptor RAGE, oxidative stress, and Ang II activates different signaling pathways and transcription factors, including NFκB, which induce the expression of pro-inflammatory, pro-fibrotic, and pro-thrombotic proteins, such as TNFα, VEGF, TGFβ, and PAI-1.
- All these processes lead to endothelial dysfunction and tissue alterations (inflammation, hypertrophy, fibrosis, apoptosis, among others), as well as organ dysfunction characteristics of neuropathy, retinopathy, neuropathy, and diabetic cardiovascular disease.

Questions and Answers

1. Endothelial dysfunction is considered as the initial step in the development of vascular complications and is induced by
   (a) Low bioavailability of nitric oxide
   (b) Uncoupled of the endothelial nitric oxide synthase
   (c) **Oxidative stress and TNFα**
   (d) Glycolysis
   (e) ATP

   TNFα induces the expression of MCP-1 and cellular adhesion molecules in the endothelium, which leads to the recruitment of leukocytes to the surface of endothelium, initiating endothelial dysfunction. Oxidative stress induces the production of TNFα and ROS reacts with NO, reducing the availability of NO as a consequence of endothelial dysfunction and the reduced availability of reduced BH4, a coenzyme required for NO synthesis.

2. The activation of PKCδ caused by hyperglycemia is dependent on
   (a) Epithelial mesenchymal transition
   (b) **Increased synthesis of diacylglycerols induced by the accumulation of trioses**
   (c) Release of the apoptosis inducing factor (AIF) from the mitochondria
   (d) Increased expression of NADPH oxidase
   (e) Direct action of TGFβ

   Diacylglycerols accumulated in the membrane activate PKCβ and PKCδ; diacylglycerols are produced from trioses accumulated during glycolysis, due to the enzyme glyceraldehyde 3-phosphate dehydrogenase inactivated by oxidative stress and the low availability of its coenzyme NAD+ as a consequence of the NADH/NAD+ imbalance.
3. The fibrosis of renal glomerulus associated with diabetic nephropathy is due to
   (a) **Increased synthesis, release, and action of TGFβ**
   (b) Increased vascular permeability
   (c) Depuration of methylglyoxal
   (d) Increased activity of antioxidant enzymes
   (e) Reduced production of Ang II

   TGFβ is a major driver for renal fibrosis, and the inhibition of TGFβ signaling significantly reduces renal fibrosis. TGFβ induces the synthesis of extracellular matrix proteins. Renal fibrosis also can be induced by AGEs, TNFα, PDGF, and chemokines in a TGFβ-dependent and TGFβ-independent manner.
4. The role of the activation of the polyol pathway in the development of diabetic complications is directly due to
   (a) Formation of diacylglycerol and activation of PKC
   (b) Formation of AGEs and chemical alteration of macromolecules
   (c) Induction of the expression of TGFβ and fibrosis
   (d) **Osmotic stress by the accumulation of sorbitol and NADH/NAD$^+$ imbalance**
   (e) Induction of the production of ROS by NADPH oxidase

   In the polyol pathway, sorbitol is accumulated as an intermediate product, because the cell membrane is impermeable to sorbitol and prevents its efflux. Sorbitol accumulation induces osmotic imbalance, water intake, and cellular death. In the second step of this pathway catalyzed by sorbitol dehydrogenase, NAD$^+$ is reduced to NADH, contributing to NADH/NAD$^+$ imbalance.
5. The role of the activation of the hexosamine pathway in the development of diabetic complications is mediated by
   (a) Induction of signaling by activation of RAGE
   (b) Formation of diacylglycerol and activation of PKC
   (c) Induction of the expression of TGFβ and fibrosis
   (d) Osmotic stress by the accumulation of sorbitol and NADH/NAD$^+$ imbalance
   (e) **Formation of UDP-N-acetylglucosamine and *O*-GlcNAcylation of proteins**

   Overproduced fructose 6-phosphate during glycolysis is used by the hexosamine pathway to the production of UDP-GlcNAc; the N-acetylglucosamine of this compound is transferred during *O*-linked glycosylation of proteins (*O*-GlcNAcylation), altering their functions and inducing the expression of TGFβ, PAI-1, and VEGF-A.
6. The role of glycation in the development of diabetic complications is due to
   (a) **Production of AGEs and activation of RAGE**
   (b) Formation of diacylglycerol and activation of PKC
   (c) Induction of the expression of TGFβ and fibrosis
   (d) Osmotic stress by the accumulation of sorbitol and NADH/NAD$^+$ imbalance
   (e) Formation of UDP-N-acetylglucosamine and *O*-GlcNAcylation of proteins.

   The effects of AGEs are mediated by the chemical modification of macromolecules or by its interaction with their receptor RAGE. The binding of AGEs with RAGE leads to the generation of oxidative stress, inducing proliferative, migratory, inflammatory, thrombotic, and fibrotic reactions, which leads to alterations associated with diabetic vascular complications.
7. Dicarbonyl stress is associated with
   (a) Accumulation of sorbitol
   (b) Accumulation of diacylglycerols and activation of PKC
   (c) **Accumulation of glyoxal and methylglyoxal**
   (d) Production of pro-inflammatory cytokines
   (e) Production of AGEs

   Glyoxal and methylglyoxal are α-dicarbonyls and reactive aldehydes, produced as by-products of glycolysis by fragmentation of triose phosphates. These aldehydes react with proteins and nucleic acid (glycation), producing endogenous AGEs, and also induce apoptosis in vascular cells fomenting endothelial dysfunction and progression of vascular complications.
8. In a microenvironment with an excessive concentration of glucose, ROS are produced by
   (a) Aldose reductase and sorbitol dehydrogenase
   (b) **Electron transport chain and NADPH oxidase**
   (c) Glutamine-fructose-6-phosphate amidotransferase
   (d) Glyceraldehyde 3-phosphate dehydrogenase
   (e) Glucose 6-phosphate dehydrogenase

   In an excessive glucose environment, the principal sources of ROS are the electron transfer chain in the mitochondria and NADPH oxidase. ROS can be produced also by other sources such as uncoupled nitric oxide synthase and xanthine oxidase.

9. Oxidative stress contributes to vascular complications by
   (a) Activation of the transcription factor NFκB and production of TNFα
   (b) Inhibition of the glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH)
   (c) Oxidative modification of macromolecules
   (d) Induction of apoptosis by DNA damage
   (e) **a, b, c, and d**

   Enhanced ROS levels induce oxidative modification of macromolecules altering their functions and cell integrity. DNA damage leads to NADH/NAD imbalance and apoptosis or necrosis. Oxidation and NADH/NAD imbalance inhibit the activity of GAPDH. Also, ROS induce several signaling pathways, including the activation of NFκB and the production of TNFα.
10. TNFα contributes to diabetic complications by
   (a) NFκB activation
   (b) Induction of NADPH oxidase expression
   (c) Promoting leukocyte recruitment at the endothelial surface
   (d) Induces apoptosis in some cells
   (e) **a, b, c, and d**

   TNFα contributes to vascular complication through multiple actions, including the induction of NADPH oxidase and increased ROS production and activation of NFκB, a transcription factor that induces the expression of pro-inflammatory cytokines and MCP-1. Also, it induces the expression of adhesion molecules promoting leukocyte adhesion at the endothelial surface.

Suggested/Further Reading

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   This review analyzes the role of hyperglycemia and glycated lipoproteins in the development of endothelial cell dysfunction (ECD) and the progression of diabetic vascular complications. The participation of dyslipidemia, oxidative and inflammatory stress, and epigenetic risk factors are highlighted, along with the specific mechanisms connecting them, as well as the new promising therapies to alleviate ECD in diabetes.
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In this study, increased markers of DNA damage by glycation in plasma and urine in patients with type 2 diabetes were detected, which were further increased in patients with diabetic nephropathy.

Glossary

Advanced oxidized protein products (AOPPs) Products of oxidative modifications of proteins by ROS and hypochlorite, derived from the action of myeloperoxidase from activated leukocytes

Dicarbonyl stress Abnormal accumulation of reactive aldehydes like methylglyoxal and 3-deoxyglucosone that leads to endogenous glycation of proteins and DNA, associated with cell and tissue damage in chronic diseases and aging

Endothelial dysfunction Alteration of the regulatory function of the endothelium on the vascular tone and properties that conduce to reduced vasodilatation and a pro-inflammatory or pro-thrombotic state

Glycation The nonenzymatic reaction between glucose and reducing sugars with amino groups of proteins, lipids, or nucleic acids leads to the production of advanced glycation products or AGEs.

Hexosamine signaling pathway Pathway activated in hyperglycemic condition, where fructose-1-phosphate, an intermediate of glycolysis, is used in the formation of UDP-GlcNAc (hexosamine pathway), followed by the *O*-GlcNAcylation of proteins

Lipid peroxidation Oxidation of polyunsaturated fatty acids by ROS in cellular membranes through free radical chain reactions, with the formation of lipid hydroperoxides as primary products; which may decompose and lead to the formation of reactive lipid electrophiles like 4-hydroxy 2-nonenal

Reductive stress Redox imbalance between NADH and NAD^+ driven by the high metabolic flux in the citric acid cycle and the activation of the polyol pathway and poly ADP-ribose polymerase

Parthanatos Mechanism of caspase-independent type of apoptosis, where the translocation to the nucleus and activity of nucleases like the macrophage inhibitory lead to DNA fragmentation and cell death

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Diabetes and Cardiovascular Disease

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Introduction

There are those who consider diabetes mellitus (DM) a cardiovascular disease since the most common and definitive final outcome with major sequelae is presented and depends on this system. In Mexico, the incidence of diabetic patients in the total number of patients treated by coronary intervention is higher than the world average, accounting for more than 40% of patients treated. Despite progress in contemporary pharmacological therapy in improving the management of diabetes and the more generalized use of statins and aspirin, the progression of atherosclerotic plaque and the regression percentage of the atherosclerotic plaque remains a prevalent issue among diabetic patients, as described by Raisuke [1]; see Fig. 50.1.

Since the 1980s, Colwell described the complexity of this problem in a classic paper [2] where he mentions that vascular disease in the diabetic patients is multifactorial with a wide myriad of derangements including endothelial, platelet, smooth muscle, lipoprotein, and coagulation abnormalities, all contributing to accelerated atherosclerosis, and has since proposed that a full understanding of the pathogenesis of this process could help design more effective preventive therapeutic approaches. The preventive approach with antiplatelet agents in the diabetic patient seems to be insufficient, since it is only focused on platelet function, forgetting the important contribution of the altered coagulation cascade in the diabetic, thrombo-fibrin, and resistance to fibrinolysis. That is why, currently there are multiple studies attempting to incorporate into the treatment of some component that improves fibrinolysis of the thrombus and thus increase the therapeutic spectrum that decreases the cardiovascular risk by this mechanism [3]. This is especially important in diabetic patients who undergo coronary intervention. Significant advances have been made in the knowledge of pathophysiology in relation to endothelial function, the role of inflammation, lipoproteins, and glucose metabolism, which begin to pro-

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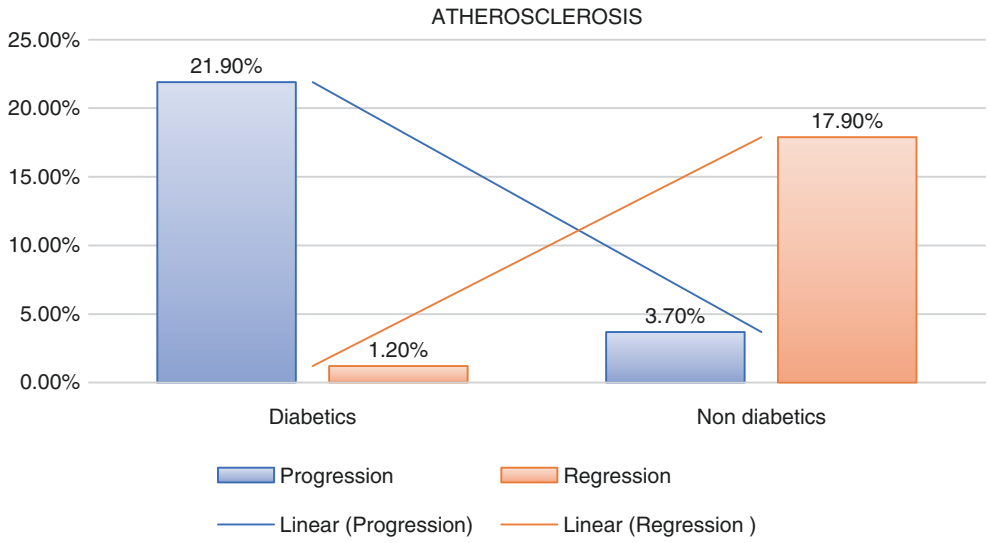

Fig. 50.1 Progression/regression of atherosclerotic plaques with contemporary treatment in patients with and without diabetes

duce concrete results in the reduction of cardiovascular risk, for example, the use of inhibitors of sodium-glucose transport proteins has shown to decrease the occurrence of cardiovascular disease and mortality, compared to other types of hypoglycemic therapies [4]. It has been possible to modulate excessive vascular response and neointimal hyperplasia after the implantation of drug-eluting stents (DES) as demonstrated in multiple studies validated with ultrasound [5]; however, the main problem in the diabetic remains the progression of new plaques in sites not treated with stents. Advances in vascular intervention have been spectacular in the last few years; noninvasive and invasive imaging technology (IVUS, OCT) has greatly aided the understanding of vascular pathology in the diabetic patients and its evolution and behavior under diverse therapeutic approaches (pharmacological stents). There is no doubt that bioabsorbable stents are already a reality as current therapeutic tools [6]; however, there are certain technological improvements that will make the clinical results, especially in diabetic patients, be equated with nondiabetics. The bet on this adventure could be the search for a platform that could treat younger or incipient plaques and seek their "cure" preventing coronary lesions from reaching irreversible states in terms of anatomy and function.

We are glimpsing the future on the shoulders of giants.

Ischemic Heart Disease in Diabetic Patients

Epidemiology

Coronary artery disease is the leading cause of death in patients with diabetes mellitus [7]. Diabetes mellitus is associated with a two- to fourfold increased risk of coronary artery disease and stroke [8–10] and with 2–3 times the risk of an acute myocardial infarction [11]. The prevalence of coronary disease increases from 2% to 4% in the general population to as high as 55% in diabetic patients [12]. The excess risk of cardiovascular disease is present in patients with type 1 diabetes mellitus and type 2 prediabetic, obese, and patients with metabolic syndrome [13]. Survival is worse in the presence of coronary artery disease, and their mortality rate is higher after myocardial infarction [14, 15]. Diabetes is present in 18–44% of patients with coronary artery disease [16–18], while in the rest, it is usual to find certain degree of dysglycemia; and previously undiagnosed diabetes can be found in up to 14–22% of patients [16]. Diabetic subjects typically have more severe coronary disease, more extensive coronary calcification, a high prevalence of left main disease, and a reduction in the recruitment of collateral circulation [19–21]. In the United States, approximately one-third of all percutaneous coronary interventions are performed in patients with diabetes, and one-quarter of patients undergoing coronary bypass surgery have diabetes [22].

Pathophysiology of Atherosclerosis (Fig. 50.2) and Endothelial Dysfunction: Metabolic Syndrome

There are several potential mechanisms through which diabetes causes accelerated formation of atherosclerotic plaques [23]; factors such as hyperglycemia, dyslipidemia, and insulin resistance lead to endothelial dysfunction [24, 25] and alterations in platelet function and coagulation [26]. All these mechanisms converge to promote plaque formation and increase its burden and complexity.

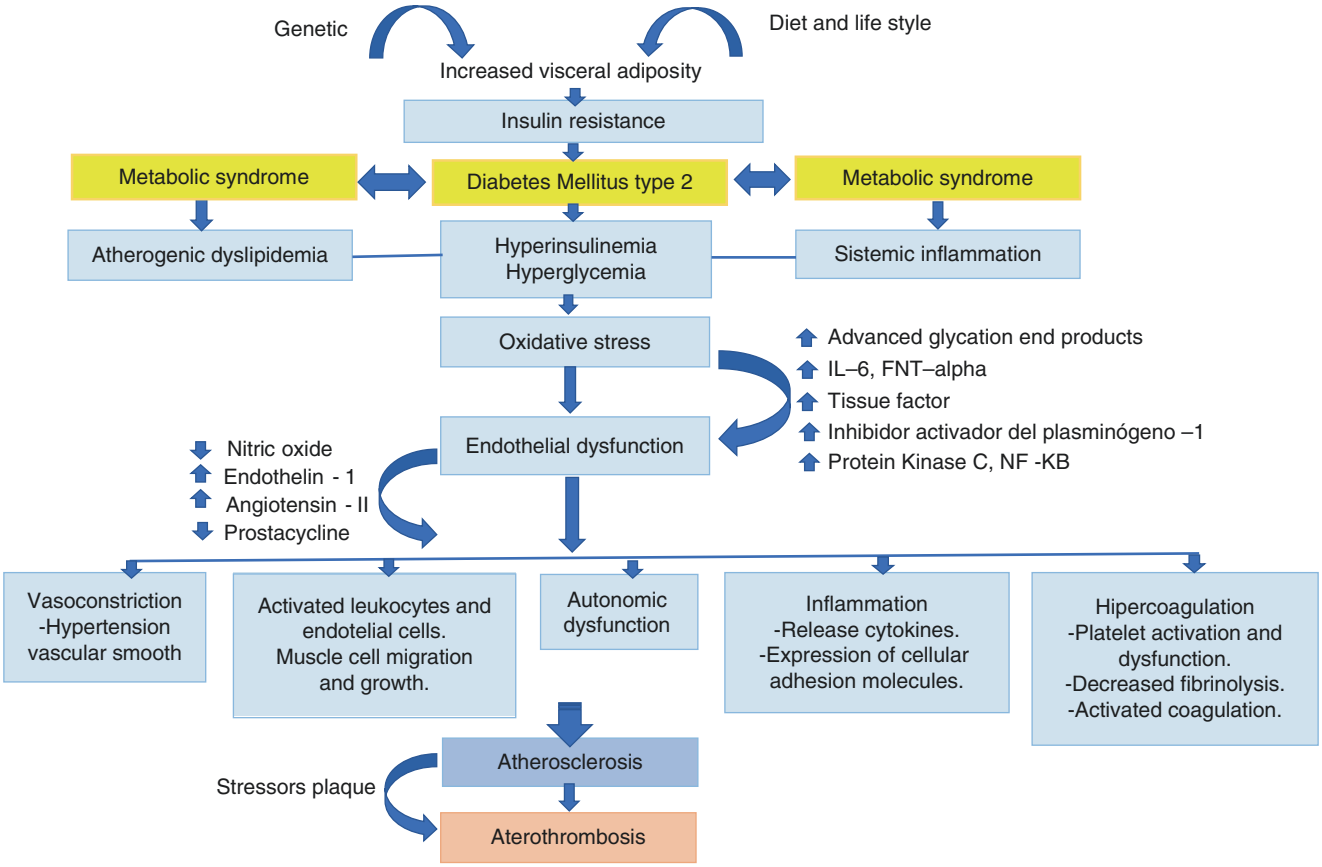

Fig. 50.2 Pathophysiology of atherosclerosis in diabetes mellitus

Treatment of Risk Factors and Its Impact on Primary Prevention

1. Hypertension Treatment: Scientific Evidence of Antihypertensive Treatment in Diabetic Patients and Lifestyle Changes and Arterial Pressure Goals in Diabetic Patients

   Hypertension is twice as common in diabetic patients as in nondiabetic patients [27]; it is postulated that hyperinsulinemia, arterial stiffness, and the expansion of extracellular volume play an important role in its presentation. This association significantly increases the risk of cardiovascular (CV) death [9, 28, 29], coronary disease [30], ventricular hypertrophy [31], heart failure [32], stroke [33], retinopathy, and nephropathy [34, 35]. Clinical trials have demonstrated the benefits of improving blood pressure (BP) [36]; thus, with each sustained reduction of 10 mm Hg in systolic blood pressure, there is a 15% reduction in the risk of cardiovascular disease, a lower risk of macrovascular and microvascular disease, and a reduction in mortality [37–39]. Diabetic patients have a higher prevalence of isolated systolic hypertension and are more resistant to treatment [40–43]. In the EUROASPIRE IV study, only 54% of patients achieved an adequate blood pressure [44]. Due to dysautonomic disorders, these patients suffer a lower reduction of nocturnal blood pressure, a higher heart rate, and a greater predisposition to orthostatic hypotension. Changes in lifestyle such as weight loss, low-sodium diet, and exercise produce beneficial effects [45]. The DASH (Dietary Approaches to Stop Hypertension) diet offers useful recommendations, such as reducing the sodium intake (<1500 mg/day), reducing the excess body weight, and increasing consumption of fruits and vegetables and low-fat foods while avoiding excessive alcohol consumption and increasing the physical activity [46]. Key management guidelines, including the Eighth Joint National Committee (JNC 8) [47] and the European Society of Hypertension and Cardiology [48], suggest that the goal of blood pressure in these patients should be less than 140/90 mmHg. Previous recommendations suggested a pressure goal of less than 130/80 mmHg. In the ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes – Blood Pressure) study, they compared intensive blood pressure control (systolic blood pressure <120 mmHg) versus standard pressure control (systolic blood pressure <140 mmHg). They found a statistically

significant reduction in the annual incidence of stroke in the intensive control group, but there were no differences in all-cause mortality and in the primary point of nonfatal myocardial infarction/nonfatal stroke/cardiovascular death. Serious adverse events were reported in the intensive treatment arm, such as a significant increase in serum creatinine above 1.5 mg/dL, hyperkalemia, hypotension, and syncope [49].

Contrastingly, the results of the recent SPRINT (Systolic Blood Pressure Intervention Trial) study, performed in patients with systolic blood pressure greater than 130 mm Hg and high cardiovascular risk, but without diabetes, showed a clear benefit in intensive treatment mortality. These results have again fanned the debate about the optimal blood pressure goal [50]. A meta-analysis, including 31 randomized studies and more than 71,000 hypertensive diabetics, reported that intensive blood pressure control significantly reduces the risk of stroke but fails to reduce the incidence of myocardial infarction or total mortality [51]. Although it is widely acceptable to achieve a systolic blood pressure <130/80 mm Hg in most diabetic patients and <140–150/90 mm Hg in elderly diabetic patients (>70–80 years), there is a lack of solid evidence to support this [52]. JNC 8 suggests that in adult White patients, the initial antihypertensive regimen should include any of the following drugs: a thiazide diuretic, a calcium channel blocker, an angiotensin-converting enzyme inhibitor (ACEI), and an angiotensin receptor blocker (BRA); in Black adult patients, a thiazide diuretic or a calcium channel blocker should be included [47]. It is usually suggested to start with ACE inhibitors or BRA as a first-line treatment because of its cardioprotective and nephroprotective effects. ACE inhibitors or BRAs should be included in the treatment of patients with chronic kidney disease, and they are contraindicated in pregnancy [53]. Generally patients require treatment with two or more drugs to meet the goal [54]. If treatment goals cannot be achieved despite the use of three different antihypertensive drugs (including a diuretic), then secondary hypertension should be ruled out. Finally, it is recommended that blood pressure should be closely monitored and treatment should be adjusted to avoid excessive falls in blood pressure [52].

2. Antiplatelet Treatment

Platelets have an important role in hemostasis and atherothrombotic disease. They are the first to initiate hemostasis. Three stages are recognized in the formation of the thrombus: (1) platelet adhesion; (2) extension, activation, recruitment, and aggregation; and (3) perpetuation and stabilization of the clot. The damaged endothelium exposes the subendothelial extracellular matrix and initiates the platelet activation mediated by the GP (glycoprotein) receptor complex Ib-IX-V which binds to vWF (von Willebrand factor). The exposed collagen also activates the platelets via GP VI and GP Ia/GP IIa. During the extension phase, platelet factors including ADP (adenosine diphosphate), TxA2 (thromboxane A2), epinephrine, serotonin, collagen, and thrombin are activated [55].

Aspirin. Its mechanism of action is by irreversible inhibition of COX 1 and 2, which decreases the production of TxA2 and PGI2. Mature platelets express only COX 1, releasing it when the TP (thromboxane receptor) is stimulated. Current guidelines recommend a loading dose of 150–300 mg of aspirin followed by 100 mg per day for life [56].

Clopidogrel. Eighty-five percent of the absorbed drug is hydrolyzed by the carboxylesterase in the liver and subsequently inactivated; the remainder 15% is converted by the CYP (cytochrome 450) in two active metabolites: 2-oxo-clopidogrel and R-130964. Recommended dose is 300–600 mg (loading dose) followed by 75 mg daily [57]. The use of a 150 mg daily dose was considered beneficial; however, the GRAVITAS study did not show benefit in the short or medium term with this dosage [58]. A 12-month clopidogrel treatment in diabetic patients with low bleeding risk who have a first-generation DES has shown to reduce the incidence of myocardial infarction and death [59].

Prasugrel. More efficient biotransformation depends on CYP3A4/5 and CYP2B6. The loading dose is 60 mg followed by 10 mg daily. It does not have as much variability as clopidogrel. TRITON – TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction) concluded higher efficacy when compared to clopidogrel, but with a higher bleeding rate including fatal bleeding. It is contraindicated in patients over 75 years of age who weigh less than 60 kg and have history of CVA (cerebral vascular accident) [60]. In those weighing less than 60 kg, half the dose can be given safely [61].

Ticagrelor. It is an oral reversible inhibitor of P2Y12 that inhibits red cell recapture of adenosine (which produces bradyarrhythmias). Its elimination is hepatic and is metabolized by the CYP3A. The loading dose is 180 mg followed by 90 mg every 12 h. It has other adverse effects such as dyspnea, hyperuricemia, and ventricular pauses ≥3 s in the first week, limiting its use [62]. Dyspnea can be the sole manifestation of angina in diabetic patients, so we need to be careful not to interpret it as a side effect of the drug.

Cilostazol. It inhibits PDE (phosphodiesterases) III increasing cAMP (cyclic adenosine monophosphate) levels in platelets, endothelium, and smooth muscle, acting as a vasodilator and anti-aggregant. The loading dose is

50 mg twice daily; if tolerated, it is increased to 100 mg twice daily. The benefits are more marked in diabetics and patients with diffuse lesions with many stents. It produces headache, tachycardia, palpitations, soft stools, and diarrhea leading to drug withdrawal in up to 15% of patients. It should be avoided in patients with heart failure [63].

European guidelines for myocardial revascularization recommend the use of Prasugrel and Ticagrelor over Clopidogrel, especially in diabetic patients, due to their lower variability and resistance, with a more stable and sustained therapeutic effect [57].

3. Lipid Treatment: Scientific Evidence of Lipid-Lowering Agents in Diabetic Patients

Multiple studies correlate high glucose and LDL (low-density lipoprotein) with atherosclerotic coronary disease. Statins are grouped according to their intensity: low intensity (simvastatin 10 mg, pravastatin 10–20 mg, pitavastatin 1 mg), moderate intensity (atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, pravastatin 20–40 mg, pitavastatin 2–4 mg), and high intensity (atorvastatin 40–80 mg, rosuvastatin 20–40 mg).

ATP (adult treatment panel) IV guidelines recommend initiating treatment as primary prevention in diabetic patients with LDL >70 mg/dL between 40 and 75 years of age with a moderate-high dose. The goal of lipid-lowering therapy for secondary prevention is a LDL <70 mg/dL [64]. Statins have shown to reduce LDL levels by 25–35% with a 4% reduction in absolute mortality and relative risk by 30% with a 42% reduction for coronary heart disease and 37% for revascularization. There is a linear relationship between LDL reduction and cardiovascular risk [65]. The Heart Protection Study demonstrated the magnitude of benefit of statins at any LDL level, reducing the rate of cardiovascular events by 24%, including diabetic patients [66].

Statins. Intensive therapy has been shown to further decrease the risk of cardiovascular death by 1.3% for all-cause mortality. The use of statins is recommended for all patients with atherosclerotic disease. Intensive therapy reduces mortality by 16%. The risk of clinical adverse events is greater in the first six months after an ACS (acute coronary syndrome). Intensive treatment reduces risk by 24% during the early stage (15–30 days), by reducing CRP (C-reactive protein) and LDL. Patients who tolerate the intensive dose should continue this dose indefinitely [67].

Niacin. HDL (high-density lipoprotein) goal as a secondary target should be >40 mg/dL. Niacin is useful for raising HDL cholesterol. There is a 1.7% risk reduction for every 1% that the HDL is increased with niacin, but its use is limited by its adverse effects. It can decrease and even reverse atherosclerosis according to the ARBITER study [68].

Fibrates. They have little benefit. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) study demonstrated that they can be combined with statins without significantly increasing adverse effects in diabetic patients, showing only benefit in nonfatal infarction and reduction of revascularization [69].

Ezetimibe. Ezetimibe binds to the Niemann-Pick receptor reducing the absorption of sterols in the intestine. It reduces LDL cholesterol by 20% when combined with statins, but there is still no evidence of benefit. So far its indication is when LDL target levels are not achieved despite intensive treatment with statins [70].

Glitazones. They stimulate the PPARG (peroxisome proliferator-activated receptor gamma) receptor improving serum glucose levels and are part of the treatment of type 2 diabetes mellitus. Pioglitazone in the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study decreased LDL/HDL by 9.5% with a nonsignificant end point reduction, but relative mortality was reduced by 16%. It increases the risk of heart failure by 41% and is contraindicated when it already exists [71].

4. Hyperglycemia Treatment: Scientific Evidence of the Impact of the Glucose-Lowering Drugs on the Cardiovascular Risk of Diabetic Patients

For the purpose of this section, we will focus on drugs that have been shown to decrease cardiovascular risk in diabetic patients. Metformin, the only drug available in the biguanide class, was studied in the UKPDS (UK Prospective Diabetes Study) trial [72], which randomized 4209 patients with newly diagnosed type 2 diabetes mellitus to receive dietary restriction or sulphonylurea or insulin treatment or metformin in overweight patients. After a ten-year follow-up, there was a significant decrease in the relative risk of death from all causes of 13% with sulfonylurea or insulin versus dietary treatment and 27% with metformin versus dietary restriction. Significant reductions in the incidence of myocardial infarction were also observed in long-term follow-up. Because metformin has been shown to be safe, is well tolerated, has low risk of hypoglycemia, is low cost, and decreases cardiovascular events, it has been proposed by international associations to be the first-line drug for type 2 diabetes in the absence of contraindications and that it can be continued after starting insulin treatment [73, 74].

Sulfonylureas are the oldest glucose-lowering drugs. They have the highest rate of hypoglycemia of all oral drugs available and favor weight gain. Tolbutamide is a first-generation sulfonylurea, which has fallen into disuse because of increased cardiovascular and all-cause mortality in a randomized study [75]; the second- and third-generation sulfonylureas have not shown to have cardiovascular adverse effects [76, 77], although some have been associated with deleterious effects in the isch-

emic preconditioning of the myocardium [78]. One of the more recent sulfonylureas, gliclazide, has been proposed as the best in this group and the only one associated with a lower risk of major adverse cardiovascular events (MACEs) and mortality, similar to metformin [79]. Cardiovascular safety of sulfonylureas was also confirmed in the UKPDS1 primary prevention study discussed above. It is important to emphasize that when these drugs are prescribed in patients with known coronary disease, dosages should be carefully adjusted to avoid hypoglycemia, which may exacerbate myocardial ischemia [80].

Regarding the thiazolidinedione group, pioglitazone showed a 16% reduction in all-cause death, myocardial infarction, and stroke at follow-up at three years in the PROactive study [81] that included 5238 diabetic patients with evidence of macrovascular disease. The efficacy of this drug in decreasing the MACE compound was corroborated in a meta-analysis of 19 clinical trials [82], with a significantly higher incidence of severe heart failure (2.3% vs. 1.8%). Similarly, two meta-analyses showed that rosiglitazone is associated with a higher incidence of myocardial infarction and heart failure, without increasing cardiovascular mortality, which led to severe restrictions in its use in the United States and its withdrawal from the market in other countries [83, 84].

Dipeptidyl peptidase 4 (DPP-4) inhibitors have discrete hypoglycemic potency and pose a low risk of hypoglycemia. In a meta-analysis of 70 phase II clinical trials of this pharmacological group, a significant reduction in the risk of MACE (OR 0.71, 95% 0.59–0.86), myocardial infarction (OR 0.64, 95% CI 0.44–0.94), and all-cause death (OR 0.60, 95% CI 0.41–0.88), but not stroke, during a mean follow-up of 44 weeks was shown [85]. In the SAVOR-TIMI (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction) study [86] that included 16,492 diabetic patients randomly assigned to saxagliptin or placebo, the drug had no effect on MACE at follow-up at 2.1 years but significantly increased the risk of heart failure from 2.8% to 3.5%. Alogliptin also failed to reduce MACE in the EXAMINE study [87] in patients with diabetes with acute myocardial infarction or unstable angina.

Recently, an inhibitor of sodium-glucose cotransporter 2 (SGLT2) called empagliflozin is demonstrated in the EMPA-REG OUTCOME trial [88], to be superior than placebo plus standard therapy in more than 7000 patients with type 2 diabetes and established cardiovascular disease. It also proved to significantly decrease the compound of cardiovascular death, myocardial infarction, and stroke by 14% and in 38% the risk of cardiovascular death, in a median follow-up of 3.1 years.

Liraglutide, a glucagon-like peptide 1 (GLP-1) agonist receptor, was compared in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial [89] versus placebo plus standard therapy in more than 9,000 patients with type 2 diabetes at high risk for cardiovascular disease or with cardiovascular disease and showed a 13% reduction in the primary MACE compound and 22% in cardiovascular death with a median follow-up of 3.8 years. Lixisenatide did not show a benefit when compared versus placebo in the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) study [90], as it failed to decrease MACE at 25 months in patients with diabetes and acute myocardial infarction in the previous 6 months.

Inhibitors of α-glucosidase may reduce the incidence of myocardial infarction; however, the evidence is still insufficient [91]. There are other hypoglycemic drugs of new pharmacological groups, available recently or in the last phases of phase III trials [92], whose impact on cardiovascular risk is still unknown.

As for insulin, in the ORIGIN study [93], 12,537 patients with impaired fasting glucose or type 2 diabetes with known cardiovascular risk factors were randomized to receive insulin glargine or the "usual" treatment (which could be insulin, oral hypoglycemic agents, or no drugs according to local practices). The primary point of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes, after a median follow-up of 6.2 years, was similar in both groups (2.94 vs. 2.85 episodes per 100 patients/year, $p = 0.63$), with higher rates of hypoglycemia and weight gain with insulin glargine and no effect on the incidence of cancer. The UKPDS [72] study also confirmed cardiovascular safety with insulin therapy. It is currently recommended to start insulin as soon as possible when blood glucose goals are not achieved with standard regimens.

The Steno-2 [94] study evaluated intensive versus conventional care strategy in the treatment of diabetic patients with microalbuminuria, with a mean follow-up of 5.5 years. The more aggressive treatment with a stepwise pharmacotherapeutic approach considering the achievement of the goals of blood glucose, blood pressure, microalbuminuria, total cholesterol and serum triglycerides, and platelet dysfunction decreased the all-cause mortality by 46% and the composite of cardiovascular events by 59%, both significantly.

In general, in diabetic patients with coronary artery disease, an HbA1c target of less than 7% is recommended according to the current ADA (American Diabetes Association) guidelines [73].

Cardiovascular Risk Evaluation in Diabetic Patients

In all patients with diabetes, the risk of atherosclerotic cardiovascular disease (ASCVD) defined as coronary death or nonfatal myocardial infarction or stroke (fatal or nonfatal) should be systematically evaluated at least every year. Among the risk factors that predispose to ASCVD are age, gender, race, diabetes, hypertension, dyslipidemia, smoking, family history of premature coronary disease (before 40 years), and the presence of albuminuria [73]. There are numerous cardiovascular risk scores, the most widely used are the American College of Cardiology/American Heart Association (ACC/AHA) ASCVD risk calculator, Framingham Risk Score, and UKPDS risk engine (which is specific for diabetic patients) named SCORE by its acronym in English Systematic Coronary Risk Evaluation. The ACC/AHA ASCVD risk tool [95] estimates the probability of having a cardiovascular event in the next ten years. It also offers treatment recommendations and is available online at http://static.heart.org/riskcalc/app/index.html.

The SCORE system [96, 97] is a simple tool that with five clinical variables estimates the risk of cardiovascular death at ten years but does not take into account diabetes since it is only considered as an independent cardiovascular risk factor after ten years of being diagnosed; this tool is available in an updated electronic version that offers treatment recommendations called HeartScore, which includes HDL cholesterol in its variables (http://www.heartscore.org).

In asymptomatic diabetic patients, routine screening studies are not recommended for coronary artery disease, as this does not improve outcomes whenever the risk factors for ASCVD are addressed [98].

Stable Ischemic Heart Disease

1. Clinical Manifestations and Risk Stratification

   Stable ischemic heart disease (SIHD) is defined as a disease that causes symptoms of angina related to stress or exercise secondary to coronary artery stenosis (≥50% in the case of the left main stem and ≥70% in one or more of the major coronary arteries) [99]. At present, "angina with normal coronary arteries" also known as microvascular angina and coronary vasospasm are also included in this definition. Usually diabetic patients with SIHD present with atypical symptoms such as non-anginal chest pain or unexplained dyspnea. Some diabetic patients may have "silent ischemic heart disease" with positive ischemia tests in the absence of symptoms. All diabetic patients with suspected SIHD should be evaluated with a probability pretest, which is based on simple clinical findings such as the pain characteristics, gender, and age [100]. In general, patients with low probability (<15%) require no additional diagnostic tests; with intermediate probability (15–85%), noninvasive ischemia-inducing studies are suggested (see next section); and in patients with high probability (>85%), invasive coronary angiography (ICA) is recommended as soon as possible, especially in the presence of severe angina at a low exercise level, with decreased LVEF (left ventricular ejection fraction) (<50%) or clinical signs of high-risk events.
2. Diagnosis

   Additional studies should be performed in search of SIHD in all diabetic patients with (1) typical or atypical cardiac symptoms; (2) in the presence of signs or symptoms of concomitant vascular disease such as carotid murmur, transient ischemic attack, stroke, claudication, or peripheral arterial disease; and (3) an abnormal resting electrocardiogram (ECG) with pathological Q waves, ST-segment, or T wave alterations suggestive of myocardial ischemia. The study most widely used is exercise ECG; however, its sensitivity is only 50%, so other noninvasive ischemia-inducing studies are currently preferred, such as exercise or vasodilator stress single photon emission computed tomography (SPECT), exercise or dobutamine or vasodilator stress echocardiography, dobutamine or vasodilator stress magnetic resonance imaging (MRI), and vasodilator stress positron emission tomography (PET), whose sensitivity, specificity, and positive and negative predictive values can be consulted in the stable coronary European clinical practice guide artery disease [99]. When patients are unable to exercise or have an ECG with complete left bundle branch block or pacemaker, then pharmacological stress with vasodilators such as dipyridamole or adenosine should be considered. Coronary artery calcium can be measured with computed tomography angiography (CTA) which is a noninvasive alternative to ischemia screening that offers a sensitivity of 95–99% and a very high negative predictive value. It also offers a very close correlation with invasive coronary angiography in terms of coronary anatomy [101]. Each of these diagnostic tests can stratify the patients in low, intermediate, or high risk which guides the decision as to whether start optimal best medical therapy (BMT) or request ICA with possible revascularization, either percutaneously or surgically.
3. Therapeutic Options
   (a) Optimal medical treatment patients with type 2 diabetes mellitus have a greater risk of developing coronary artery disease (CAD) than nondiabetic patients [102]. In addition, 75% of patients with T2DM die as a result of cardiovascular diseases, including CAD [12]. In patients with T2DM, CAD tends to be more complex characterized by multivessel disease, small

vessels, and calcified and diffuse lesions and are occasionally requiring additional coronary revascularization to control angina [103–105]. Current medical management emphasizes the importance of controlling risk factors, including successful blood glucose control and treatment with statins, angiotensin receptor blockers/angiotensin-converting enzyme inhibitors, and antiplatelet therapy [106]. Guidelines for the management of diabetes mellitus of the American Diabetes Association, the American College of Cardiology, and the American Heart Association recommend the following prevention strategy for coronary artery disease: blood pressure of 130/80 mm Hg or less, low-density lipoprotein cholesterol (LDL-C) below 70 mg/dL for patients with CAD, and immediate smoking cessation [107, 108]. In large-scale studies to assess clinical outcomes comparing revascularization and intensive medical management (COURAGE, BARI-2D, and FREEDOM), the one-year goal compliance rate to achieve LDL-C levels <100 mg/dL, systolic blood pressure <130 mmHg, glycosylated hemoglobin <7.0%, and smoking cessation was 18%, 23%, and 8%, respectively.

(b) Revascularization treatment. Recent advances in techniques and devices used in coronary interventional procedures have extended the indication of PCI toward more complex lesions. Drug-eluting stents (DES) have reduced restenosis and reintervention rates [108–110], although the mortality of CAD in patients with T2DM remains high.

Most clinical trials comparing the outcomes of patients with type 2 diabetes mellitus and multivessel coronary artery disease have shown that coronary artery bypass grafting (CABG) is superior to balloon angioplasty and angioplasty with bare metal stents (BMS) in terms of target vessel revascularization, myocardial infarction, and mortality.

More recently, the use of new scales to analyze angiographic and clinical variables (SYNTAX II, Euro SCORE II) has been proposed for a better decision-making process in revascularization strategies [111], particularly in patients with T2DM who will require a multidisciplinary discussion taking into account the patients' coronary anatomy, the characteristics of the lesions, age, and comorbidities.

Several clinical trials are currently being conducted in 85 centers in the USA and Europe that compare CABG with percutaneous coronary intervention (PCI) with drug-eluting stents. The "SYNergy between coronary intervention and cardiac surgery" (SYNTAX) study was a prospective randomized study comparing the efficacy of CABG and PCI with paclitaxel-releasing stents in patients with complex coronary artery disease [112]. In this study, 25.1% of the patients were diabetic. In the cohort of diabetic patients, the incidence of major coronary events and cerebrovascular disease at three years was 37.0% in the PCI group and 22.9% in the CABG group ($p = 0.002$). The incidence of target vessel revascularization was also higher in the PCI group when compared to CABG (28.0% vs. 12.9%, $p < 0.001$) [113].

In 2012, the FREEDOM study randomized a total of 1900 diabetic patients with multivessel coronary disease to CABG and PCI using mainly sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) [114]. All-cause mortality and myocardial infarction were significantly lower in the CABG group when compared to the PCI group (18.7% vs. 26.6%). However, most patients in the PCI group were treated with first-generation DES. The use of new-generation DES, particularly everolimus-eluting stent, is changing the outcomes mainly because of a reduction in the incidence of stent thrombosis and myocardial infarction [115].

Recently, Banglore et al. published a meta-analysis of 68 randomized trials that compared the clinical outcomes of patients with CAD and diabetes revascularized with CABG versus PCI with DES, including sirolimus, paclitaxel, and everolimus-eluting stents [116]. All-cause mortality was higher in patients who were treated with sirolimus-eluting stents and paclitaxel-eluting stents compared to CABG. Meanwhile mortality rates between everolimus-eluting stents and CABG were similar. Bioabsorbable scaffolds are a new alternative that could have potential advantages over drug-eluting stents in terms of adverse coronary events. Muramatsu and colleagues compared bioabsorbable stents versus everolimus-eluting stents in diabetic patients in different clinical trials and reported that the incidence of cardiac mortality, myocardial infarction related to the treated vessel, and target vessel revascularization was similar with both types of stent (3.9% vs. 6.4%, $p = 0.38$) [117, 118].

Acute Coronary Syndromes

1. Clinical manifestations and diagnosis. Coronary disease is very common in the diabetic population; up to 32% of patients with acute coronary syndrome have diabetes mellitus [119]. Myocardial ischemia diagnosis can be challenging in diabetic patients [120, 121]. Physical

examination findings are variable and may be related to hemodynamic instability, electrical instability, or mechanical complications. Physical examination may rule out a different source of chest pain. A fundamental diagnostic aid is the 12-lead electrocardiogram, which must be acquired immediately in these patients [122]. This study may have discrete changes in more than 30% of patients and is less sensitive if there are alterations in intraventricular conduction [123, 124]. Cardiac biomarkers help in confirming the diagnosis and guiding the treatment, in addition to stratifying the risk. Troponins are more sensitive and specific, and their determination is fundamental for decision-making [125–127]. Measurement of CK-MB and copeptin is also useful [128–130]. Angiography is indicated if the suspicion of ACS is high; in other cases, coronary angiotomography may be performed. Other methods, such as echocardiography, magnetic resonance imaging, and cardiac nuclear test, complete the evaluation and diagnosis [131].

2. Risk stratification. The initial presentation characteristics are helpful markers for early prognosis; resting chest pain, heart failure, and mitral regurgitation are associated with a poorer prognosis [132]. There are many variables and scales that assess the risk of death; these scales are not always easy to apply. The TIMI risk score is a useful risk assessment tool in cases of myocardial infarction and ST-segment elevation amenable to reperfusion therapy [133]. High levels of high-sensitivity troponin are associated with an increased risk of death. A high serum creatinine and low glomerular filtration rate pose a grim prognosis to these patients; these variables are included in the Global Registry of Acute Coronary Events (GRACE) [134] and assess the risk of death or the combination of death and myocardial infarction at six months. This score showed that coronary revascularization is independently associated with better survival at one year in cases of acute coronary syndrome without high-risk ST-segment elevation; the same benefit was not observed in low- or intermediate-risk groups [135, 136]. The SYNTAX score uses angiographic criteria to make clinical decisions and thus estimate the likelihood of long-term cardiovascular and cerebral events in patients undergoing surgical or percutaneous revascularization; it predicts outcomes such as death, infarction and CVA and needs for revascularization, or the combination of all, in patients with surgical or percutaneous revascularization, based on the complexity and extent of coronary lesions. A low SYNTAX score is <22 points, intermediate from 23 to 32, and high when it is >33. Higher scores show better long-term outcomes with surgery [137, 138]. It is essential to evaluate the risk of bleeding in the treatment of myocardial infarction without ST-segment elevation. A controlled trial of patients with coronary artery disease of two or three vessels, randomized to revascularization surgery versus percutaneous treatment with drug-eluting stents, showed a significant decrease in all-cause mortality in the surgical revascularization group [139]. This finding was consistent with the SYNTAX trial. The CRUSADE scale quantifies the risk of major intrahospital bleeding [140].

3. Medical Treatment:
   (a) Glucose control in the context of an ACS and glucose goals and insulin therapy. Medical treatment in the acute phase of an acute coronary syndrome is similar in patients with and without diabetes mellitus. Patients with acute coronary syndrome and diabetes mellitus are the group with the highest death rate, myocardial infarction, recurrent ischemia, and CHF (congestive heart failure) during follow-up [141]. There is a close relationship between glucose levels and mortality in this group of patients. Both hyperglycemia and hypoglycemia have adverse effects on inhospital outcomes and mortality. The NICESUGAR study showed that intensive glucose control increased mortality in adults in intensive care: serum glucose of 180 mg/dL or less resulted in lower mortality than if it was 81–108 mg/dL [142]. There is no established role for the administration of glucose-insulin-potassium infusions in NSTE (non-ST-elevated myocardial infarction)-ACS.
   (b) Antiplatelet agents. Aspirin should be given to any patient with suspected or diagnosed acute coronary syndrome. When no contraindication exists, it should be started early. If there is any contraindication for its use, then clopidogrel should be started. Patients treated with early invasive reperfusion should receive the combination of aspirin with some P2Y12 inhibitor. Inhibitors of GP IIb/GP IIIa receptors in patients with acute coronary syndrome without ST-segment elevation are associated with a reduction in mortality at 30 days, particularly in patients with diabetes mellitus undergoing percutaneous revascularization. Several trials have shown the benefit of oral antiplatelet therapy in these patients with a reduction in ischemic events without an increase in bleeding complications with the use of prasugrel compared to clopidogrel [143]. In PLATO study, ticagrelor showed less ischemic events regardless of diabetic state and glycemic control, without increased bleeding than clopidogrel [144].
   (c) Renin-angiotensin-aldosterone antagonists. Optimal treatment in these patients includes the use of a renin-angiotensin-aldosterone antagonist, particularly in patients with heart failure and ejection fraction less than 40%. Patients intolerant to angiotensin-converting enzyme inhibitors should receive angiotensin receptor blockers as a class I indication.

(d) Beta-blockers. They should be used in the first hours after the diagnosis of an acute coronary syndrome, provided there are no contraindications to it. If there is contraindication in the acute phase of the infarction, it can be reevaluated in the following hours.

(e) Anticoagulation. The combination of anticoagulation with antiplatelet therapy is recommended regardless of the initial treatment. Enoxaparin, bivalirudin, fondaparinux, and unfractionated heparin are among the recommended anticoagulants. Enoxaparin significantly reduces the recurrence of ischemic events and the need for invasive procedures; this benefit was sustained for up to 1 year [145], although other studies did not demonstrate a significant difference in death or myocardial infarction at 30 days when comparing this drug with unfractionated heparin [146]. Anticoagulation with bivalirudin alone suppresses ischemic events similar to the use of heparin plus glycoprotein IIb/glycoprotein IIIa inhibitors while at the same time significantly reducing the risk of bleeding complications [147–149].

(f) Statins should be initiated or continued in all patients, with and without diabetes mellitus in the context of an acute coronary syndrome, provided there is no contraindication; they reduce the recurrence of infarction, coronary disease mortality, cerebral vascular event, and the need for revascularization.

(g) Nitrates. If chest pain persists, then sublingual nitroglycerin can be administered; if there is no improvement, it can be administered intravenously, as in the case of heart failure.

(h) Calcium channel blockers. They are an alternative to avoid the recurrence of ischemia or when there is contraindication to the use of beta-blockers, provided there is no left ventricular dysfunction or altered atrioventricular conduction. They are also indicated in patients with coronary spasm [150].

4. Revascularization therapy in acute coronary syndromes:

(a) Percutaneous coronary intervention (PCI) in ST-elevated myocardial infarction (STEMI).

The frequency of coronary events requiring primary intervention is well known. The impact of diabetes mellitus on the outcomes of patients with ST-segment elevation infarction since the onset of primary angioplasty has been well established. It was first described by the Mayo Clinic and Columbia University group [151], who concluded that despite similar TIMI 3 flow rates in patients with and without diabetes, patients with diabetes are more likely to have perfusion abnormalities assessed with the reduction of the ST-segment and myocardial blush; it is also contemplated that the reduction of myocardial perfusion after primary angioplasty may contribute to an increase in mortality in this population. Persistent ST elevation and abnormal myocardial blush in the presence of normal epicardial flow are indicative of decreased microvascular flow also known as a "non-reflux" phenomenon [152]. These alterations of the microvasculature are much more frequent in the diabetic population. Several mechanisms have been postulated for which diabetes contributes to microvascular damage. First, diabetes is associated with a prothrombotic and inflammatory state, accumulation of leukocytes, and thrombus formation in the capillaries of diabetics which leads to coronary microvascular obstruction [153].

Many studies have compared the impact of type 2 diabetes mellitus (T2DM) on prognosis in postcoronary intervention patients. In a recent meta-analysis published in 2016 [154] which included patients from the HORIZONS-AMI [155] trial and 12 other studies of which 7 were randomized controlled trials, 4163 patients were analyzed for major adverse cardiovascular events (MACE) and myocardial infarction (MI) and 17,015 patients analyzed for mortality. There was a significant increase in the rate of MACE and MI in the group of non-insulin-treated diabetes mellitus compared to the non-insulin group (OR: 1.63, 95% CI (1.17–2.27) $p = 0.04$) (OR: 1.82, 95 % CI (1.08–3.06) $p = 0.02$). These differences are also reflected in mortality. Recently published in 2017 is the largest cohort that includes patients with STEMI [156], from the UK and Wales health systems. This cohort of patients with STEMI included 281, 569 patients of which 120, 568 were patients with diabetes mellitus. STEMI with diabetes compared to patients with STEMI without diabetes were more prone to have a previous infarction (34.9 vs. 22.5%), heart failure (10.5 vs. 5.8%), and chronic renal failure (11.3 vs. 4.6%). After this cohort was adjusted for age, sex, and years of diagnosis, DM was associated with a 72% increase in the risk of mortality (1.72, 95% CI 1.66–1.79) for STEMI. The reperfusion rates managed for this cohort were 73.1% versus 79% in patients without DM.

In the final analysis, there were over 1,944,194 person years at risk, the median time to death was 2.3 (IQR 0.9–4.2) years, and 200, 360 (28.4%) died. At all-time points from hospitalization with AMI, unadjusted cumulative relative survival was significantly worse among patients with diabetes (log rank tests $p < 0.001$).

(b) Percutaneous coronary intervention (PCI) in non-ST-elevated myocardial infarction (NSTEMI).

Diabetics have a higher incidence of multivessel CAD. In the American registry CRUSADE (Can

Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines), the prevalence of diabetes was 33% among 46,410 patients with non-ST-elevation ACS. The PRESTO [157] trial showed that compared to NDM, patients with T2DM had an advanced age were mostly female patients and the majority had a history of heart failure and lower ejection fraction. These patients with T2DM were mainly overweight and obese and had a high rate of comorbidities. The FREEDOM [158] trial showed that in patients with diabetes and multivessel coronary artery disease, MACEs were higher in patients treated with insulin compared to patients without insulin therapy. Revascularization trends in patients with diabetes and patients with diabetes and multivessel CAD presenting with NSTEMI, ACTION Registry: 29,769 patients enrolled from July 2008 to December 2014. Overall, 36.4% were treated with CABG, 46.2% received PCI (77.2% with at least one DES), and 17.3% were treated with no revascularization. The proportion of patients receiving any kind of revascularization increased from 81.1% to 83.6% (PP < 0.0001 for trend), driven entirely by hospital-level use of CABG. Despite guidelines recommending CABG over PCI for diabetics with multivessel CAD, only about one-third of them actually receive CABG in the setting of NSTEMI. Accelerated atherosclerosis, atherosclerotic plaque rupture, and increased platelet activity, all of which increase the incidence of acute MI compared to nondiabetics. In the current propensity-matched analysis of contemporary real-life data, an early invasive strategy was associated with an increased inhospital survival in NSTE-ACS patients with concomitant DM. These results support the 2014 ACCF/AHA guideline recommendations for an early invasive strategy in diabetics, especially those with high-risk features (e.g., NSTEMI and cardiogenic shock). Meanwhile, the use of this strategy in lower-risk patients, such as those with UA (unstable angina), may not be associated with improved survival [159]. The incidence of inhospital mortality also was lower with an early invasive strategy in the secondary post-hoc analysis using a tighter match tolerance (2.5% vs. 3.7%; OR, 0.65; 95% CI, 0.56–0.75; $P < 0.0001$) and in the sensitivity analysis after excluding the patients with length of hospital stay less than 48 h in the propensity-matched cohort (2.1 vs. 3.3; OR, 0.63; 95% CI, 0.56–0.72; $P < 0.0001$). On subgroup analysis, the benefit of an early invasive strategy was demonstrated among a wide range of prespecified subgroups except in patients with UA, where there was no apparent evidence of survival benefit with an early invasive strategy (0.5% vs. 0.1%; OR, 7.86; 95% CI, 0.82–75.72; $P = 0.07$), with evidence of heterogeneity when compared to NSTEMI patients (P interaction=0.02). Diabetes was also associated with a significantly higher mortality at one year for both presentations (HR 1.7 and 1.2, respectively). At one year, patients with diabetes presenting with non-ST-elevation ACS had a risk of death that approached that of nondiabetic individuals presenting with STEMI (7.2% vs. 8.1%). In the TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)-TIMI 18 trial, an early invasive strategy was associated with a significant 22% reduction in the relative risk of death, MI, or rehospitalization for ACS at six months compared with an early conservative strategy [160].

(c) Fibrinolytic therapy in STEMI.

Regarding to fibrinolytic therapy, a meta-analysis of the Fibrinolytic Therapy Trialists' Collaborative Group, which included all the large randomized trials of fibrinolytic therapy versus placebo in STEMI, demonstrated a greater survival benefit at 35 days among diabetic patients compared with nondiabetic individuals, corresponding to 3.7 lives and 1.5 lives saved per 100 patients treated, respectively. While CABG in the setting of STEMI is typically reserved for failed PCI and for MI-related mechanical complications, primary PCI may be preferred over thrombolytic therapy in diabetic patients. However, the data to support this notion are limited [161]. A pooled analysis of individual patient data from 19 randomized trials comparing primary PCI with fibrinolysis for the treatment of STEMI included 6315 patients, 877 (14%) of whom had diabetes. The 30-day mortality rate (9.4% vs. 5.9%; $P < 0.001$) was higher in patients with diabetes. Mortality was significantly lower after primary PCI compared with fibrinolysis in both patients with diabetes (unadjusted OR 0.49; $P = 0.004$) and those without diabetes (unadjusted OR 0.69; $P = 0.001$) [162].

Complete ST resolution at 90 minutes after fibrinolytic therapy has been shown to be less prevalent between diabetic patients when compared with nondiabetic patients [163].

(d) Coronary artery bypass grafting (CABG).

The impact of diabetes on morbidity and mortality in patients undergoing surgical coronary revascularization was remarked in a retrospective analysis of the Society of Thoracic Surgery database, including 41,663 diabetic patients among a total population of 146,786. At 30 days, the mortality was significantly higher in the diabetes group (3.7% vs. 2.7%). The

unadjusted and adjusted mortality OR (odds ratio) for diabetes were 1.4 and 1.2, respectively. With respect to diabetes treatments at presentation, the adjusted mortality OR for patients on oral hypoglycemic drugs and on insulin were 1.1 and 1.4, respectively. In addition, the overall morbidity and the infection rates were significantly higher among diabetic patients. Looking into long-term mortality following CABG, a prospective cohort study including 11,186 consecutive diabetic patients and 25,455 nondiabetic patients undergoing CABG from 1992 to 2001 detected a significantly higher annual mortality rate among diabetic patients (5.5%) compared with nondiabetic individuals (3.1%).The annual mortality increased to 8.4%, 16.3%, and 26.3% among diabetic patients with vascular disease, renal failure, or both, respectively. In addition to increased periprocedural morbidity and mortality as well as long-term mortality, diabetic patients must undergo repeat revascularization following CABG more frequently than their nondiabetic counterparts [164].

Heart Failure in Diabetic Patients

Introduction and Epidemiology

Cardiovascular death is the leading cause of death among patients with diabetes mellitus. The diabetic population is at higher risk of developing heart failure (HF) compared to the nondiabetic population, so diabetes mellitus (DM) is considered an independent risk factor for the development of HF, where a 1% increase in glycosylated hemoglobin increases the incidence of heart failure from 8% to 16% [165].

Bell et al. found that of 5757 patients with chronic HF treated with carvedilol, 25% had diabetes mellitus [166]. In an analysis of the European Heart Failure Pilot Survey which included 3226 patients with chronic HF, the prevalence of diabetes was 29%, and it was associated with older age, higher NYHA functional class, and predominance of ischemic HF etiology. The study concluded that DM is an independent predictor of death and hospitalization due to heart failure [167].

Pathophysiology

The development of heart failure in the diabetic patient is considered multifactorial, associated mainly with coronary disease, accelerated atherosclerosis, metabolic disorders, small vessel disease, and diabetic cardiomyopathy [168].

Diabetic cardiomyopathy was first described in 1972 when Rubler et al. [169, 170] found left ventricular dilation in the absence of ischemic heart disease in autopsies of diabetic patients. In this context, diabetic cardiomyopathy was clinically defined by the presence of structural alterations or abnormal myocardial function in the absence of hypertension, coronary disease, and valvular disease. The presence of diabetic cardiomyopathy is not essential for the development of HF in the diabetic patient.

The key for the development of HF is hyperglycemia, which leads to lipotoxicity, free fatty acid oxidation, oxidative stress, and apoptosis (apoptosis and myocardial cell necrosis is greater in the diabetic patient than in the nondiabetic patient). Other contributing factors are the constant activation of the renin angiotensin-aldosterone system, sympathetic nervous system (SNS), activation of proinflammatory cytokines, and formation of advanced glycosylation products. All of these in a greater or lesser degree lead to fibroblast proliferation and collagen deposits ultimately causing interstitial and perivascular fibrosis, the main features of diabetic cardiomyopathy [171–173]. Endomyocardial biopsy studies have found an increase in type III collagen deposits but not of type I and IV collagen in patients with type 2 DM. Others show collagen distribution patterns characterized by collagen types I and III at the perivascular level and IV at the endocardium. In both humans and animals, an increase in cardiac fibrosis has been found even before the onset of hyperglycemia [174, 175].

The end products of advanced glycosylation (EPAG) are derived from a nonenzymatic irreversible reaction between sugars and proteins, called the Maillard reaction. It is considered to play an important role in the pathophysiology of heart failure. It has been associated with endothelial dysfunction, development of atherosclerosis, diastolic dysfunction, and in advanced stages systolic dysfunction. EPAG can be covalently bonded to each other, resulting in the formation of additional bonds between matrix proteins such as collagen, laminin, and elastin. This type of binding increases the stiffness of the protein matrix and leads to diastolic dysfunction; the presence of EPAG has been associated with increased isovolumetric relaxation time and left ventricular diameter [176].

The alterations in sympathetic innervation, characteristic of diabetic neuropathy, have been associated with HF, due to alterations in the expression and activation of catecholamines and increased activation of beta 1 receptors, resulting in apoptosis, fibrosis, and ventricular dysfunction. Markers of diabetic neuropathy such as HRR (altered heart rate recovery) are associated with the development of heart failure in the diabetic patients [177].

1. Left ventricular hypertrophy (LVH) and diabetes mellitus.

   The association between left ventricular hypertrophy and DM has been controversial and has been explained by

other mechanisms, such as hypertension [178]. In the Northern Manhattan Study (NOMAS) [179], ventricular mass was determined with transthoracic echocardiography. DM was shown to be an independent risk predictor for the development of left ventricular hypertrophy (adjusted odds ratio 1.46, 95% CI, 1.13–1.88, $P = 0.004$), after adjusting for age, sex, race, mass index (BMI), systolic BP, education, history of coronary artery disease (CAD), physical activity, and alcohol consumption. There was also a direct interaction between abdominal circumference and LVH ($P = 0.01$) which translates the close relationship between insulin resistance, activation of RAAS (renin-angiotensin-aldosterone system), SNS activation, and left ventricular hypertrophy in the diabetic patient with and without arterial hypertension [180, 181]. Cardiac magnetic resonance has broadened our understanding of diabetic cardiomyopathy, demonstrating fat infiltration, fibrosis, altered ventricular geometry, and ventricular mass increase. Patients with HF have higher NT-BNP (N-terminal pro-B-type natriuretic peptide) levels than nondiabetic patients, with no difference in other biomarkers.

2. From diastolic dysfunction to symptomatic HF.

The spectrum of diabetic heart disease is broad and varies from normal heart, subclinical diastolic dysfunction, and systolic dysfunction (detectable only by imaging techniques) to symptomatic heart failure.

Diastolic dysfunction is present in up to 50% of the diabetic population and has a close relationship with the levels of glycosylated hemoglobin and diabetic microangiopathy [181]. Systolic dysfunction is a late appearing condition. Fang et al. found that up to 24% of asymptomatic diabetic patients had systolic dysfunction determined with echocardiographic Doppler and Strain imaging [182].

This subclinical dysfunction in the absence of silent coronary disease and left ventricular hypertrophy has been related to glycosylated hemoglobin levels. In a study that included 219 patients, Flag et al. found that 16% had systolic dysfunction and 21% had diastolic dysfunction. The independent predictors of systolic dysfunction were glycosylated hemoglobin levels ($p < 0.001$) and lack of pretreatment with angiotensin-converting enzyme inhibitors (ACEI) ($p = 0.003$) and for diastolic dysfunction the absence of treatment with insulin ($p = 0.008$), treatment with metformin ($p = 0.01$), age ($p = 0.013$), and arterial hypertension ($p = 0.001$) [183]. Thus, the mechanisms involved with the development of heart failure depend on the control of diabetes, type of treatment implemented for both diabetes control and blockade of the renin-angiotensin-aldosterone system, and other associated factors such as age and hypertension. From et al. showed that 23% of a 1760 patient cohort had diastolic dysfunction. The cumulative five-year HF development in these patients was 36.9%, compared to 16.8% in patients without diastolic dysfunction ($p = 0.001$). Diabetic patients with diastolic dysfunction had a significantly higher mortality rate than those without diastolic dysfunction. This association was independent of the presence of arterial hypertension, coronary disease, or other echocardiographic parameters [184].

The RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) trial which included diabetic and nondiabetic patients with HF and preserved systolic function showed that diabetic patients ($n = 93$) were significantly younger, obese, and more frequently males and had a higher prevalence of hypertension, renal failure, lung disease, and vascular disease. Levels of uric acid, C-reactive protein, galectin-3, collagen I, and endothelin-1 were significantly higher in diabetic patients ($p < 0.05$). Diabetic patients had lower functional capacity and a significant increase in the risk of hospitalization for renal and cardiac causes (23.7% vs. 4.9%, $p < 0.001$) [185].

BNP is a good prognostic and diagnostic marker in diabetics with HF. Van Der Horst et al. demonstrated that the diabetic population with HF has higher levels of natriuretic peptides than the nondiabetic population ($p = 0.03$), being a predictor of mortality, along with norepinephrine, in diabetic patients with advanced HF [186].

Prevention and Treatment of HF and DM

HbA1c levels > 7% are associated with an increased risk of hospitalization for HF in patients with type 2 DM [187]. The STENO II trial [94] showed that intensive glucose treatment (glycosylated Hb <6.5%) and risk factor treatment (arterial pressure <130/80 mmHg, triglycerides <150 mg/dL, total cholesterol <175 mg/dL) were associated with a reduction in CV death and infarction and need for revascularization. However, other studies such as UKPDS [188], ACCORD, ADVANCE, and VADT (Veterans Affairs Diabetes Trial) showed no benefit between intensive glucose treatment and HF [189].

The blockade of the renin-angiotensin-aldosterone system is a cornerstone in the high cardiovascular risk patient; in the HOPE study, 38% of the population was diabetic; the use of ramipril was associated with a reduction in the relative risk of HF (9.2 vs. 11.7 OR 0.77, $P < 0.001$), as well as a lesser development of de novo diabetes with a 32% risk reduction ($p = 0.002$) [190]. In the EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Patients with Stable Coronary Artery Disease) study in diabetic patients treated with perindopril, there was a reduction in hospitalization for HF [191].

Empagliflozin is a potent and selective inhibitor of sodium-glucose cotransporter (SGLT2) used in the treatment

of type 2 DM. By inhibiting SGLT2, empagliflozin reduces renal glucose reabsorption and increases urinary glucose excretion. In addition to reducing hyperglycemia, empagliflozin is associated with osmotic diuresis, natriuresis, weight loss and visceral fat and blood pressure reduction, albuminuria with neutral effect on the sympathetic nervous system, and other favorable effects on the markers of arterial stiffness and vascular resistance [192]. The EMPA-REG OUTCOME study showed that empagliflozin reduced hospitalization and death from heart failure [2.8 vs. 4.5%; HR: 0.61 (0.47–0.79); $P < 0.001$] and was associated with a reduction in all-cause hospitalization [36.8% vs. 39.6%; HR: 0.89 (0.82–0.96); $P = 0.003$], arousing the discussion of HbA1c as the main therapeutic objective to reduce cardiovascular events, leaving the door open to other mechanisms involved in reducing cardiovascular death and hospitalizations for HF beyond of the strict HbA1c targets [193].

Patients with diabetes and HF in the PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor Neprilysin Inhibitor] With ACEI [Angiotensin-Converting Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial treated with a combination of sacubitril/valsartan had a greater long-term reduction of HbA1c than those receiving enalapril. The de novo use of insulin was 29% lower in patients receiving sacubitril/valsartan ($p = 0.0052$). These data suggest that sacubitril/valsartan may improve glycemic control in patients with diabetes and HF [194].

Pharmacological treatment of the patient with HF with and without diabetes mellitus should include ACE inhibitors, beta-blockers, and aldosterone blockers. Similar benefit has been seen in patients treated with carvedilol in both diabetic and nondiabetic patients (RRR 28% $p = 0.03$ and 37% $p < 0.001$, respectively). There was no significant difference between reducing the risk of death or NNT (number needed to treat) in patients treated with diabetes versus nondiabetics [166].

In the DIG (Digitalis Intervention Group) study, 28.4% of the patients had diabetes. In this study, the addition of digoxin to the treatment of HF reduced hospitalizations secondary to HF without a substantial increase in the risk of toxicity. However, in patients with HF treated with digoxin, it is necessary to identify predictors of toxicity, and strict control of serum levels is important to maintain their benefit [195].

Diseases of the Aorta in Diabetic Patients

Diabetes and Aortic Dissection/Aneurysm

Aortic dissection along with intramural hematoma and penetrating ulcer of the aorta comprise the acute aortic syndromes [196]. Acute aortic dissection is the result of spontaneous tear of the intima, followed by passage of blood between the intima and the aorta. This passage of blood generates a false lumen that progressively compresses the true lumen of the vessel. Clinically, it manifests as an acute and penetrating thoracic pain of sudden onset and of immediate maximum intensity with irradiation toward the back. Pathophysiologically, diabetes mellitus contributes to thickening and fibrosis of the intimal layer and degradation and apoptosis of smooth muscle cells in the media. These processes lead to necrosis and fibrosis of the elastic components of the arterial wall, which in turn produces wall stiffness and weakness, from which dissection and rupture may arise [197]. Although diabetes mellitus does not have a direct causal role in aortic dissection, its role in the development of atherosclerosis contributes to the risk of aortic dissection. Interestingly, a recent study published by Xe et al. demonstrated a paradoxical inverse relationship between DM and risk of aortic dissection in Chinese patients, suggesting that diabetes may play a protective role in the development of aortic dissection. Despite these findings, further information is necessary to elucidate the role of diabetes in aortic dissection [198, 199].

Aortic aneurysm refers to the pathologic enlargement of an aortic segment which tends to progress over time and generally cause no symptoms until they rupture. Atherosclerosis was believed to be the main factor for the development of aortic aneurysms, but recent evidence has shown that aneurysms represent a systemic disease of the vasculature associated with inflammation, smooth muscle cell apoptosis, and matrix degradation. Male gender, hypertension, smoking, and hypercholesterolemia are the main risk factors associated with aortic aneurysms [200]. Diabetic patients with aortic aneurysms are significantly less likely to present with rupture or to die from aneurysm rupture when compared to nondiabetic patients with aortic aneurysms. It is plausible that DM may have a protective effect on aortic aneurysm rupture. Again, further evidence is needed to prove this [201].

Treatment of both aortic dissection and aneurysms is complex and depends on many factors such as hemodynamic status, localization, and anatomical features, all of which are beyond the scope of this chapter.

Diabetes and Aortic Stenosis

Aortic stenosis is the most common primary valve disease in the developed world. It is characterized by a progressive narrowing of the aortic valve orifice due to degeneration, fibrosis, and calcification of the aortic leaflets [202]. This degenerative process has been associated with advanced age and atherosclerosis. Clinically, it manifests with angina, dyspnea, and syncope. A one-year survival among patients with severe aortic stenosis is approximately 50% [203].

Echocardiography is the key diagnostic tool. Aortic peak velocities >4 m/s with mean aortic gradients >40 mm Hg are consistent with severe aortic stenosis regardless of the aortic valve area (severe is >1 cm^2).

Diabetes mellitus has been associated with multiple aspects of aortic stenosis such as the following:

1. Increased inflammation: Patients with diabetes mellitus have accelerated inflammation which leads to calcification. This calcification appears earlier and is more severe than in nondiabetic patients.
2. Stenosis progression. Aortic valve area narrowing is faster in diabetic patients as a result of increased calcium and fibrotic deposits on the valve.
3. Heart failure: As mentioned previously in this chapter, diabetes contributes to left ventricular hypertrophy and with time to systolic dysfunction. The aortic valve stenosis potentiates this effect accelerating the decline in the contractile function of the heart [204].

Aortic valve replacement is the treatment of choice for patients with severe aortic stenosis. Diabetic patients with micro- and macrovascular complications (renal failure, coronary heart disease, neuropathy) have a higher surgical risk based on STS (Society of Thoracic Surgeons) score and EuroSCORE (European System for Cardiac Operative Risk Evaluation) II than nondiabetic patients. Percutaneous implant of an aortic valve (TAVI) has recently shown to be a safe and effective alternative to surgery in high-risk and intermediate-risk patients [205].

Arrhythmias in Diabetic Patients

Special Features of Arrhythmias and Atrioventricular Blocks in Diabetic Patients

In 1972, Rubler [169] introduced the term diabetic cardiomyopathy (DCM) to refer to structural and functional abnormalities of the myocardium in diabetic patients without coronary artery disease, systemic arterial hypertension, or any other morbid entity that affected the functioning of the heart. Interstitial and perivascular fibrosis is the histological landmark of the disease; hypertrophy of cardiomyocytes has also been described, although it does not appear to be a requirement [206]. The loss of normal microvasculature and remodeling of the extracellular matrix are involved and the systolic and diastolic contractile dysfunction of diabetic hearts. It is possible that in DM the increase in fibrosis is involved in the degeneration of the conduction system which may result in an increase in symptomatic bradycardias. Podlaha [207] found the presence of DM in 49.2% of patients with pacemakers and only 38.4% in nondiabetic patients of the same age, gender, and comorbidity. Perhaps more than the degeneration of the conduction system, DCM-related interstitial fibrosis has a greater impact on the progression of ventricular remodeling, which may result in delayed left ventricular depolarization with increased QRS associated with intra- and interventricular dyssynchrony. The response to cardiac resynchronization therapy does not appear to be different between diabetic and nondiabetic patients, but mortality is higher among the first [208]. At the atria, interstitial fibrosis in patients with DCM may also be secondary to oxidative stress, growth factors, and changes in cellular binding proteins [209]. Overall, fibrosis and atrial remodeling have been identified as primary elements in the generation and maintenance of atrial fibrillation (AF) in patients with DCM [210].

Atrial fibrillation is the most frequent sustained cardiac arrhythmia in clinical practice and is one of the most important determinants of increased cardiovascular morbidity and mortality in patients with heart disease and DM. Numerous studies have shown that poorly controlled DM is associated with new-onset AF [211, 212]. Huxley et al. showed that in patients without diabetes, there is a linear trend between the presence of AF and 1% increments in the level of HbA1c [213]. In diabetic patients, HbA1c levels above 6.5% are associated with a 40% increase in the risk of AF presentation especially in women [214].

Although DCM contributes to cardiovascular disease, the one factor that directly increases the risk of mortality is the development of autonomic diabetic neuropathy (ADN). In diabetic patients with severe ADN, the sympathetic-parasympathetic innervation imbalance may contribute to death by ventricular arrhythmias both in the absence and in the presence of ischemic heart disease [215]. Also, in diabetic patients, sympathetic denervation has been shown to be predictive of sudden death, due to a decrease in the ventricular arrhythmogenic threshold, which has greater expression during events of hypoglycemia or metabolic alterations related to hyperglycemia [216]. The prevalence of ADN is estimated to be as high as 50% in diabetic patients [217]. It is possible that at the initial stages of ADN, there is an increase in sympathetic tone which manifests as tachycardia, shortening of QRS and QT interval, increase in QT dispersion, and flattening of T wave. In advanced states, neurological denervation can lead to an increase in the parasympathetic tone that subsequently increases the risk of developing bradycardia, prolongation of QTc, and other alterations in repolarization [218]. During iatrogenic hypoglycemia, prolongation of the QT interval associated with calcium overload and potassium depletion may also lead to ventricular fibrillation risk. The poor sympathetic response to hypoglycemia is not enough to counteract the electrocardiac effects; on the contrary, it may represent a synergic proarrhythmic effect by increasing repolarization alterations [219].

Multiple Choice Questions

1. Pathological mechanisms associated with increased risk of coronary atherosclerosis in patients with diabetes include:
   (a) Vasoconstriction and hypertension of vascular smooth muscle
   (b) Activation of leukocytes/endothelial cells, release of cytokines, and expression of cellular adhesion molecules
   (c) Autonomic dysfunction
   (d) Hypercoagulation
   (e) *All of the above*
2. All of the following statements about diabetic patients are true, except:
   (a) Compared to nondiabetic, patients with diabetes have two- to threefold higher rate of coronary disease and are at increased risk of myocardial infarction, congestive heart failure, and death.
   (b) Compared to nondiabetic, patients with diabetes have twofold higher rate of systemic arterial hypertension.
   (c) The current guidelines suggest that therapeutic target of blood pressure control is less than 140/90 mmHg.
   (d) Antihypertensive treatment in patients with chronic renal disease should include an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.
   (e) *The majority of patients require only one antihypertensive drug to achieve the goal blood pressure*.
3. If a patient tolerates the intensive dose of a statin, what is the best option to do next?
   (a) Increase the dose until the patient starts with secondary effects.
   (b) *Decrease the dose until LDL is over 70 mg/dL.*
   (c) Keep the dose.
   (d) Decrease the dose until HDL starts falling.
   (e) Add ezetimibe in all cases.
4. Dyspnea may be caused by which antiplatelet agent:
   (a) Aspirin
   (b) Clopidogrel
   (c) Prasugrel
   (d) *Ticagrelor*
   (e) Ticlopidine
5. In diabetic patients, what drug has been approved as first-line hypoglycemic drug to reduce cardiovascular events?
   (a) Gliclazide
   (b) Metformin
   (c) Alogliptin
   (d) *Empagliflozin*
   (e) Pioglitazone
6. In diabetic patients with known coronary artery disease, an HbA1c target of less than ___ is recommended:
   (a) 6%
   (b) 6.5%
   (c) 6.8%
   (d) *7%*
   (e) 7.5%
7. What is the most frequent sustained cardiac arrhythmia and one of the most important factors in the increase of cardiovascular morbidity and mortality in patients with diabetes?
   (a) Ventricular fibrillation
   (b) *Atrial fibrillation*
   (c) First-degree AV block
   (d) Third-degree AV block
   (e) Atrial flutter
8. What drug was associated with a reduction in the incidence of heart failure?
   (a) Ramipril
   (b) Sacubitril/valsartan
   (c) Carvedilol
   (d) *Spironolactone (aldosterone antagonist)*
   (e) All of the above
9. Which of the following risk factors is not associated with aortic aneurysms and may have a protective effect on aortic aneurysm rupture?
   (a) Male gender
   (b) Hypertension
   (c) Smoking
   (d) Hypercholesterolemia
   (e) *Diabetes*
10. In general, what is the preferred method of coronary perfusion in patients with an acute coronary ischemic syndrome, with or without diabetes?
   (a) Fibrinolytic therapy
   (b) Coronary artery bypass grafting
   (c) *Percutaneous coronary intervention*
   (d) Aspirin
   (e) Statins

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Diabetes and Stroke: The Role of Glucose Regulation

51

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Stroke as a Long-Term Complication of Uncontrolled Diabetes Mellitus

Introduction

The relationship between stroke and diabetes mellitus (DM) though complex is undeniable. Numerous studies have delineated a clear correlation between prediabetes, diabetes mellitus type 1, and diabetes mellitus type 2 as they relate to cerebrovascular disease with decades of research detailing the causality between hyperglycemia and stroke risk. The global prevalence of stroke continues to rise despite the advances in treatment options for cardiovascular risk factor modification such as diabetes. Diabetics represent a subset of the patients who are at 2–3 times higher risk of mortality from stroke than the general population [1]. The purpose of this chapter is to look over essential epidemiological concerns about DM and stroke and mainly to detail the microvascular and macrovascular mechanisms that promote cerebrovascular disease in diabetics which leads to stroke. Subsequently, the remarkable role of hyperglycemia in acute ischemic stroke will be revised. Additionally, the importance of glucose control for both primary and secondary stroke prevention will be discussed in terms of the role of therapeutical options for attaining normoglycemia. Finally, there will be in-depth discussion of the optimization of diabetic control as it relates to other stroke risk factors such as atherosclerosis, hypertension, and atrial fibrillation.

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Epidemiological Overview of Diabetes and Stroke

In 2019, according to the global burden of disease collaborators, stroke remains as the second leading cause of death and the third leading cause of death and disability combined (as measured by disability-adjusted life-years [DALYs]) in the world [2]. DM is included within the five leading specific risk factors contributing to stroke DALYs, with a population attributable fraction (PAF) of 20.2% (95% uncertainty intervals [UIs] 13.8–29.1) of all stroke DALYs. It should be noted that among cerebrovascular diseases, DM is usually associated with the ischemic stroke type (PAF 19.5% [(10.6–34.6)]), ranking as the third most important risk factor for this type of stroke. However, in the last years, it is becoming evident that DM is also associated with hemorrhagic strokes: the PAF for intracerebral hemorrhage is 17.3% (11.2–24.8) and for subarachnoid hemorrhage of 16.8 (11.0–23.4), ranking as the fourth and five most important risk factors, respectively, for these stroke types.

The large increase in the global burden of stroke is probably not only due to population growth and aging but also because of the substantial increase in exposure to several important risk factors such as high BMI, high fasting plasma glucose, high systolic blood pressure, and low physical activity. DM is among the risk factors with an outstanding increase in the age-standardized stroke PAF from 1990 to 2019 (from 14.4% to 20.2%), corresponding to a 40.3% increase. In other words, if high fasting plasma glucose exposure were reduced to its theoretical minimum risk exposure level, there would be a 20.2% reduction in stroke in 2019 [2].

Microvascular Complications of Diabetes

Diabetes mellitus is a modifiable risk factor for ischemic stroke and is defined by one of the following: a fasting blood glucose (fbg) of ≥ 126, a hemoglobin A1C (HbA1C) of ≥ 6.5%, 2 h postprandial glucose of ≥ 200 mg/dL after

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administration of a 75 g glucose tolerance test, or a random serum glucose ≥ 200 mg/dL in a patient with classic signs of hyperglycemia/hypoglycemia [3]. The pathophysiology of DM is complex and its interrelation with the development of cerebrovascular disease is well studied. However, the microvascular and macrovascular changes that occur due to persistent hyperglycemia have not been fully elucidated. Microvascular changes within cerebrovasculature and systemic vasculature occur through multiple cellular pathways that are directly modulated by fluctuations of serum glucose.

Microvascular changes due to hyperglycemia, which are noted on both the cellular and genetic levels, occur due to a chronic, systemic, inflammatory state induced by the production of reactive oxygen species (ROS) with early changes noted on both the cellular and genetic levels. The sources of the ROS are diverse and include excess superoxide production via mitochondria, direct oxidation of serum glucose, endothelial cell nitrogen oxygen synthase (eNOS), NADPH (nicotinamide adenine dinucleotide phosphate) oxidase activation from abundance of advanced glycosylation end products (AGEs) [4], and the upregulation of mitochondrial matrix metalloproteinase (MMP-9) [5]. The dysfunction of microvascular endothelium begins to occur via these pathways in addition to many others that are far less well understood and mimic the changes found in the vasculature that is exposed to chronic inflammatory processes.

Chronic hyperglycemia causes abnormal production of ROS from normal glycolytic processes that metabolize glucose and results in excess side products including ROS which overwhelm the cellular antioxidants such as superoxide dismutase and glutathione peroxidase. To prevent continued production of ROS, many systemic cells will downregulate glucose transporters (GLUTs). However, endothelial cells normally express non-insulin-dependent GLUTs which allows for continued intracellular glycolytic generation of ROS. In addition to continued generation of ROS via glycolysis, mitochondrial dysfunction begins to occur with persistent hyperglycemia inducing a chain reaction during which multiple intracellular pathways are activated leading to further endothelial dysfunction [4].

Electron transport chain uncoupling within mitochondria propagates unmitigated binding of ROS to available intracellular oxygen further promoting oxidative stress. Indeed in numerous studies, it has been shown that inhibition of ROS production within endothelial mitochondria prevents the cumulative oxidative endothelial cell dysfunction in the setting of hyperglycemia. Apoptotic events, genetic expression of pro-inflammatory markers, and nitrogen oxide inhibition are all mitigated by inhibition of mitochondrial free radical production due to hyperglycemia [3]. In one study, Mishiro et al. demonstrated that the mitochondrial involvement in endothelial cell dysfunction is more complex than previously discerned in that hyperglycemia not only disrupts normal metabolic processes but also alters mitochondrial membrane permeability to the point of self-induced organelle apoptosis, MMP-9 production, and death of endothelial cells comprising the cerebral microvasculature [5].

Advanced glycation end products (AGEs) are byproducts of glycosylated proteins or lipids that normally occur in the presence of hyperglycemia. The exact mechanism by which AGEs are derived is via the Maillard reaction which in short produces ketoamine that form AGEs via a dual pathway. In the setting of sustained hyperglycemia such as that which exists in diabetes mellitus or even in prediabetic states, these AGEs accumulate rapidly and are deposited within various tissues. Receptors for advance glycosylation end products, RAGE, exist in normal endothelial cells and not only can prevent endothelial cell repair but also promote infiltration of the vascular endothelium by inflammatory cells. Activation of RAGE and its promoted binding to AGE in DM causes endothelial cell dysfunction which manifests in some DM patients as diabetic microangiopathy [6]. However, not all AGE-related endothelial cell dysfunction are RAGE dependent [4].

RAGE-independent endothelial dysfunction can occur due to glycation of LDL (low-density lipoprotein), extracellular cell matrix proteins, or activation of signaling proteins other than RAGE [4]. Kim et al. noted that AGE overproduction causes excessive LDL modification as well as increased expression of CD36 ligands [7]. This CD36 expression occurs predominantly in monocytes and blunts the inflammatory reaction that occurs in DM patients who experience endothelial cell injury thereby inhibiting proper endothelial repair [7]. Similarly, in the setting of hyperinsulinemia commonly present in DMII patients, macrophages derived from monocytes demonstrate insulin receptor dysfunction which is pro-atherogenic in the setting of an already compromised endothelial integrity [8].

It is also important to note that other inflammatory proteins such as monocyte chemoattractant protein-1 (MCP-1) and IL-6 are also upregulated in diabetics with the elevation of MCP-1 causing both increased macrophage recruitment and increased adipocyte insulin resistance. In fact, many inflammatory markers such as C-reactive protein (CRP), intracellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1) are overexpressed in hyperglycemia not only in the diabetic but also in normal subjects who experience impaired glucose tolerance (IGT) or postprandial hyperglycemia [9]. Persistent hyperglycemia in DMII leads to concomitant improper physiologic response yielding a state of chronic hyperinsulinemia due to insulin resistance which in and of itself is disruptive to the integrity of cerebrovascular endothelium [8].

In animal studies involving cardiac endothelium, per Bornfeldt et al., hyperinsulinemia led to downregulation of

insulin-mediated endothelial pathways that promote alteration of endothelial gene expression and production of transmembranous proteins [8]. Sustained elevation of serum insulin causes saturation of insulin receptors and increased activation of 3-phosphoinositide-dependent protein kinase 1 (PDK1) which through a series of reactions promotes increased transcription of metabolic genes [8]. The epigenetic and genetic changes induced by chronic hyperglycemia can persist even years after serum glucose is controlled [10]. Consequently, these metabolic genes allow for increased rates of glycolysis, lipid synthesis, and GLUT (glucose transporter) production. Additionally, when vascular smooth muscle cells are exposed to hyperinsulinemia, they demonstrate activation of pathways influenced by insulin-like growth factor-1 receptors (IGF1R) that are known to be proatherogenic [8]. All of these pathways, as noted in Fig. 51.1, lead to ROS overproduction, glycolysis upregulation, and genetic modifications.

Disruption of vasculature endothelium at the microvascular level in diabetics is most commonly seen in diabetics in the form of complications such as microangiopathy, arterial retinopathy, nephropathy, and peripheral neuropathy. Moreover, emerging evidence has demonstrated that cerebral microvascular dysfunction and damage in DM are common as depicted mainly by MRI (magnetic resonance imaging) showing typical features of cerebral small vessel disease [11]. Indeed, microvascular involvement of other known areas such as retinal microvascular abnormalities in patients with type 2 diabetes correlates with the presence of cerebral small vessel lesions [12]. Optimal brain function depends on a healthy microvasculature including the delivery of nutrients and removal of waste products in response to changes in neuronal activity maintaining the interstitial milieu for proper function of the so-called neurovascular unit (a complex interaction of several cell types including endothelial cells, astrocytes, pericytes, and neurons). In addition, cerebral microvasculature is a crucial site of the blood-brain barrier that protects the neurons from external factors and maintains the internal milieu within the CNS (central nervous system) highly regulated and also decreases and stabilizes the pulsatile hydrostatic pressure at the level of capillaries and participates in the cerebrovascular reactivity and cerebral autoregulation that regulates and maintains global brain perfusion. Cerebral microvascular dysfunction

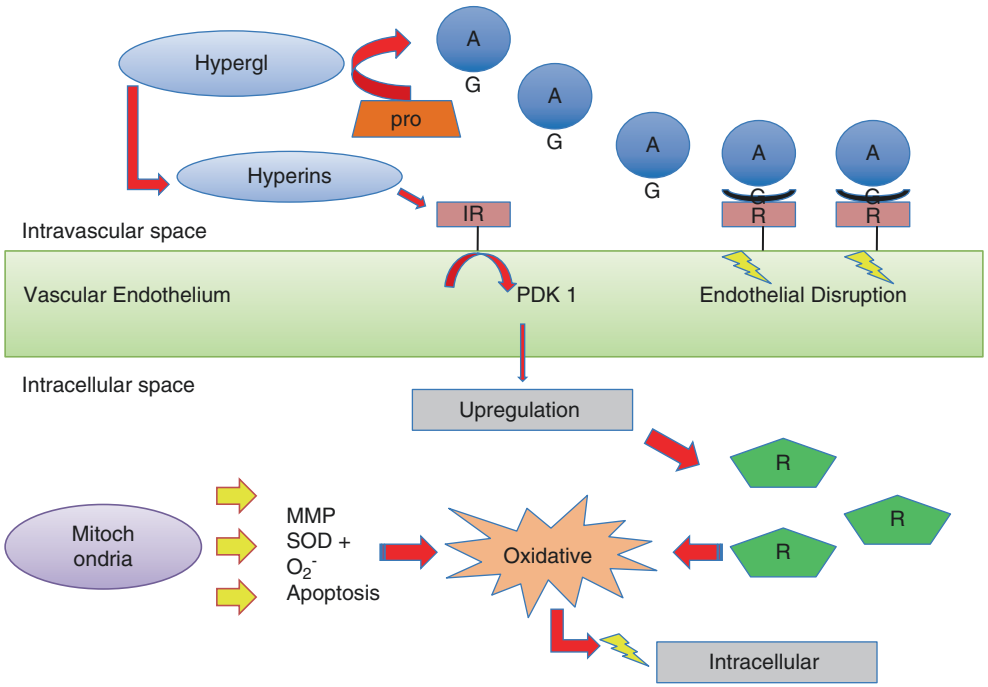

Fig. 51.1 Process of hyperglycemia-induced vascular endothelial dysfunction. Chronic hyperglycemia causes glycosylation of both fats and lipids resulting in the production of advanced glycosylated end products (AGEs). AGEs bind to receptors for advanced glycosylation end products resulting in endothelial disruption. Hyperglycemia results in concomitant hyperinsulinemia that can cause oversaturation of insulin receptors as well as overproduction of 3-phosphoinositide-dependent protein kinase (PDK1). PDK1 overproduction causes upregulation of glycolysis and subsequent overproduction of reactive oxygen species (ROS). Mitochondrial dysfunction under the influence of chronic hyperglycemia can result in overproduction of mitochondrial matrix metalloproteinase (MMP-9), superoxide dismutase, and organelle-induced apoptosis. All of these mitochondrial products as well as glycolytic-induced ROS lead to oxidative stress resulting in intracellular dysfunction, abnormal metabolic gene transcription/upregulation allowing for increased rates of glycolysis, lipid synthesis, and GLUT transporter production. *AGE* advanced glycosylated end products, *RAGE* receptor for AGEs, *PDK1* 3-phosphoinositide-dependent protein kinase, *IR* insulin receptor, *MMP* mitochondrial matrix metalloproteinase, *SOD* superoxide dismutase, and *ROS* reactive oxygen species

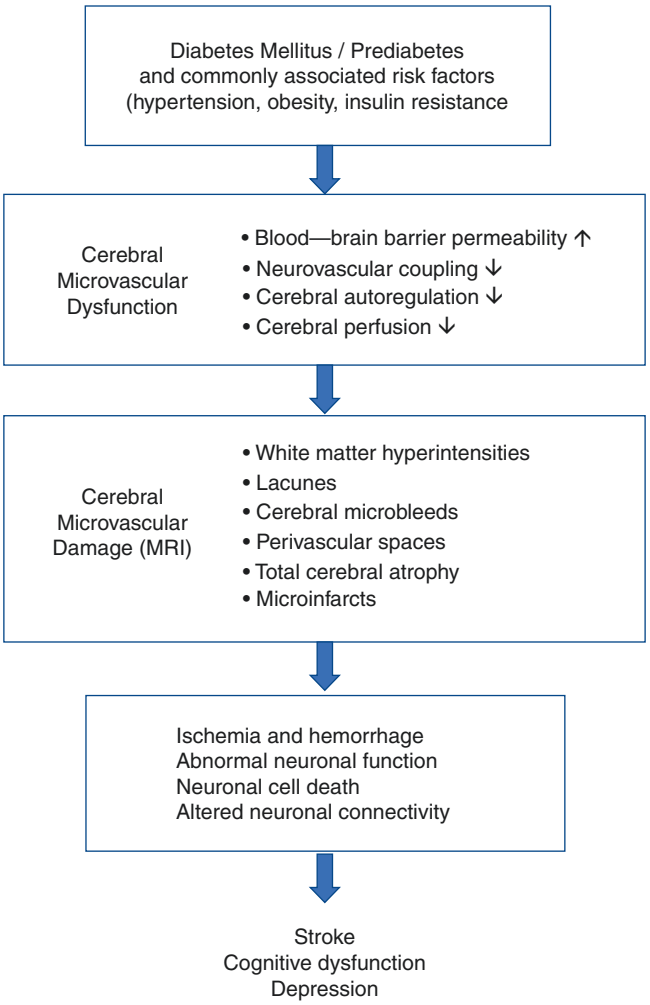

Fig. 51.2 Assumed pathway by which type DM-related cerebral microvascular dysfunction contributes to stroke and other mental disorders such as cognitive dysfunction and depression. Prediabetes and DM and commonly associated risk factors (hypertension, obesity, and insulin resistance) induce cerebral microvascular damage and dysfunction including an increase of permeability of the blood-brain barrier and decrease of neurovascular unit coupling and cerebral autoregulation as well as reduction of cerebral perfusion. These abnormalities give rise to the typical features of cerebral small vessel disease as depicted by MRI (see Fig. 51.3) and manifested clinically as stroke, cognitive disorders, and depression. (Modified from Fig. 2, [11])

may be defined as an impairment in any of these previous functions. Figure 51.2 summarized the assumed pathway by which type 2 diabetes-related cerebral microvascular dysfunction contributes to stroke and other mental disorders such as cognitive dysfunction and depression [11]. Figure 51.3 shows illustrative lesions of small vessel disease commonly observed by MRI in patients with diabetes.

Furthermore, microvascular complications were initially delineated in the landmark UK Prospective Diabetes Study (UKPDS). This was the first comprehensive study to demonstrate that strict regulation of serum glucose levels can prevent microvascular complications of hyperglycemia [13]. The data derived from this prospective study of DMII patients noted that over a period of ten years if aggressive glucose control was achieved via sulphonylurea or insulin administration, there was a significant reduction in microvascular complications regardless of intervention. Up to a 25% reduction in nephropathy and ophthalmic complications was noted in the patient arm randomized to receive intensive serum glucose control. Additionally, the final average HbA1C of patients under intensive glucose control was 11% lower with a median value of 7% which directly corresponded to an improved rate of microvascular complications in that study arm. No macrovascular benefit was observed in either study arm nor were significant deleterious macrovascular outcomes [13].

Further studies such as the Action to Control Cardiovascular Risk in Diabetes Mellitus (ACCORD) evaluated whether even more aggressive serum glucose control than that achieved by patients in UKPDS would further prevent microvascular disease. However, the ACCORD study with its target HbA1C of 6% was stopped prematurely due to a significantly increased mortality rate in the intensive therapy treatment arm [14]. Unsurprisingly, it was noted in the Heart Outcomes Prevention Evaluation (HOPE) trial that concomitant treatment of hypertension and hyperlipidemia (HLD) in diabetics leads to improved outcomes with significantly decreased frequency of microvascular complications [15]. These significant interactions between hyperglycemia and hyperlipidemia as they relate to increased risk of ischemic stroke on the microvascular level are complex and exist in both the prediabetic and diabetes mellitus patients.

As mentioned in the preceding paragraphs, persistent hyperglycemia activates the AGE/RAGE complex. Interestingly, the blockade of the excess activation of the ligand/receptor complex decreases atherosclerotic formation as well as diabetic nephropathy in hyperglycemia [9]. Increased production of vascular smooth muscle cells (VSMCs) is also encouraged during periods of hyperglycemia and has been demonstrated in DMI and DMII. Though the pathways responsible for atherosclerotic formation in diabetics are not fully understood, it is likely that vascular endothelial injury is caused by hyperglycemia which is directly responsible for creating a pro-inflammatory state promoting VSMC proliferation, microangiopathy, and microvascular changes [16]. It is this pro-inflammatory state created by hyperglycemia that forces endothelial cells such as those present in the retinal vasculature to overexpress factors such as vascular endothelial growth factor (VEGF) in order to survive in an ischemic environment [9]. According to Prasad et al., VEGF also was found in animal studies to increase vascular permeability resulting in microvascular changes as well as compromise of the blood barrier itself even in the setting of only transient hyperglycemic events [17].

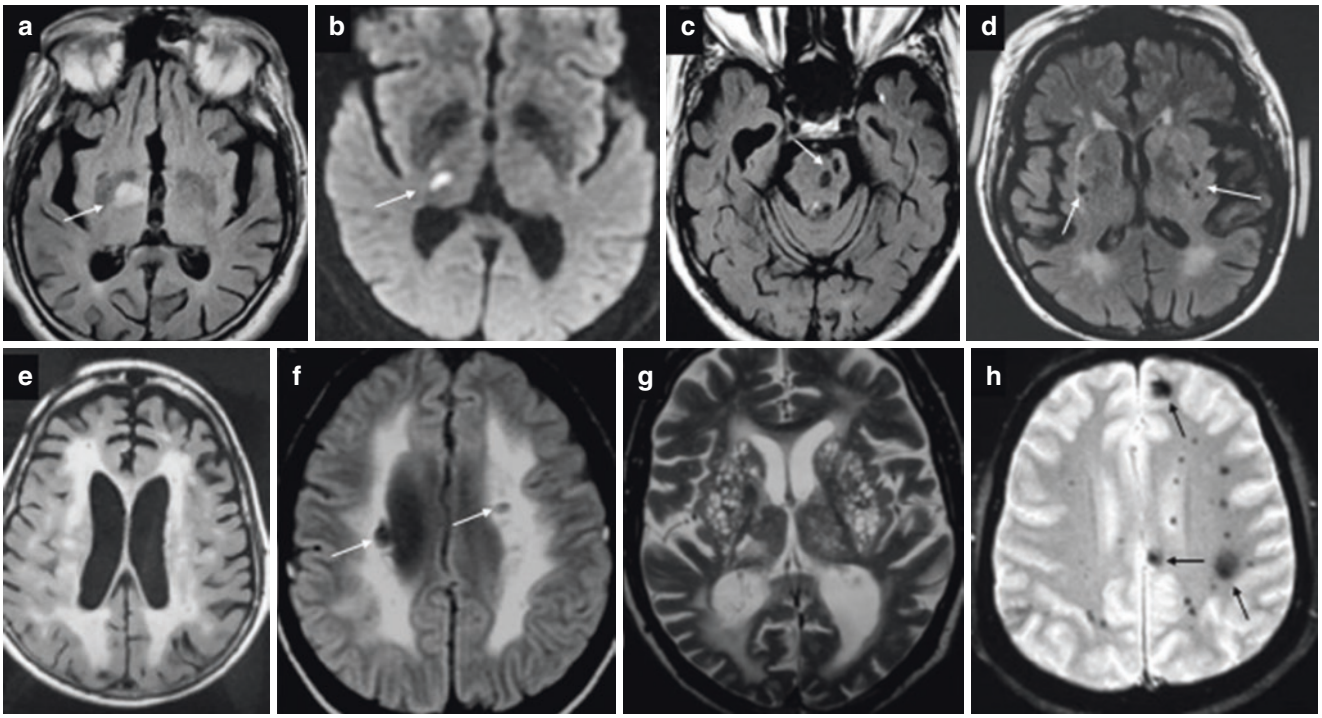

Fig. 51.3 MRI imaging characteristics of features of cerebral small vessel disease commonly seen in patients with diabetes. (**a**) FLAIR sequence depicts a thalamic lacunar infarct (arrow). (**b**) Diffusion-weighted shows a hyperintense lesion corresponding to an acute small deep (lacunar) infarct (arrow): less than 2 cm diameter. (**c**) T1-weighted imaging with a hypointense lesions in the pons corresponding to old lacunar infarcts (arrow). (**d**) FLAIR sequence showing multiple small deep lacunar infarcts (arrows). (**e**) FLAIR imaging of typical large confluent areas of white matter hyperintensities (WMH) extending from the periventricular to the center of the bilateral semioval tissues. (**f**) FLAIR imaging of WMH similar to (**e**) but including hypointense lesions (old lacunar infarcts) within the WMH (arrows). (**g**) Extensive areas of perivascular spaces on T2-weighted imaging are hyperintense because they contain CSF-like fluid, less than 3 mm diameter, seen bilaterally in the basal ganglia. (**h**) Multiple foci of microbleeds within cortex and subcortical structures on gradient-echo T2 imaging (larger lesions with arrows)

Macrovascular Complications of Diabetes

Macrovascular changes due to hyperglycemia have been shown to result in neointimal expansion after the initial endothelial injuries have begun to accumulate within the diabetic patients. Normal vascular neointimal healing and formation are adversely affected by hyperglycemia creating systemic vasculature that is abnormally thickened by abnormally proliferating VSMCs [18] leading to noncompliant vasculature, hypertension, and increased stroke risk. Involvement of multiple cerebrovascular territories including vasculature to the blood brain barrier is also compromised in the setting of hyperglycemia with dysfunction of arterial smooth muscle elasticity leading to stenosis, ischemia, and stroke [19]. Other animal studies demonstrate that cerebral arterioles likely undergo deleterious changes to endothelium more rapidly than larger cerebrovasculature such as the basilar or carotid arteries [20]. According to Zhou et al., animal studies in which arterial injury was created via balloon dilatation resulted in hyperplasia of the neointima likely due to a pro-inflammatory vascular environment from both hyperglycemia and hyperinsulinemia [21]. In summary, these animal studies demonstrating the microvascular and macrovascular effects of hyperglycemia and atherosclerosis were later partially confirmed in several human trials. The Action in Diabetes and Vascular Disease (ADVANCE) trial showed that microvascular events were significantly decreased in diabetics though the mitigation of macrovascular complication did not reach significance. The targeted HbA1C of the ADVANCE (Action in Diabetes and Vascular Disease-PreterAx and DiamicroN Controlled Evaluation) trial was 6.5% in the intensive treatment arm with the most significant benefit evident in the rate of nephropathy complications which were decreased by 21%. Later trials including the Veterans Affairs Diabetes Trial (VADT) as well as the Diabetes Control and Complications Trial (DCCT) also demonstrated similar results in short-term monitoring of the intensive treatment arms in both studies again showing significant improvement in microvascular outcomes with non-significant macrovascular event decrements. However, after longitudinal follow-up in the DCCT patients, it was determined that patients in the intensive glucose control arm did, in fact, demonstrate a significant reduction in ischemic car-

diac diseases, strokes, or CV deaths (n = 711 patients in intensive treatment arm vs. n = 730 in conventional treatment arm, p = 0.02) [20]. This was in agreement with prior data that noted diabetics were up to ten times more likely to suffer CAD (coronary artery disease), peripheral vascular disease (PVD), or stroke compared to nondiabetics [22].

DM and Hyperglycemia in Acute Ischemic Stroke

One of the conditions adversely affecting outcome in patients with acute ischemic stroke is hyperglycemia. Hyperglycemic diabetic patients admitted to the hospital for acute ischemic stroke are up to two times more likely to die within the first month compared to normoglycemic patients. Lau et al. [23], in a meta-analysis of 39 studies, report a significant relationship between DM and mortality, and poor neurological and functional outcomes. They also found an association with length of hospital stay, readmission rate, and stroke recurrence. Also, the Get With The Guidelines Stroke registry found a similarly significant association between acute ischemic stroke patients with DM and mortality as well as readmission three years post-discharge in an analysis of 409,060 American patients with cerebral ischemia including transient ischemic attack [24]. Several factors may potentiate the increased risk of stroke in DM patients, including endothelial dysfunction, arterial stiffness, and systemic and local inflammation. Also, diabetes and postischemic acute hyperglycemia are likely to be associated with poor reperfusion and recanalization outcomes due to several factors including vascular injury, clot composition, and impaired collaterals; and then, hyperglycemia appears to interfere with the efficacy of reperfusion therapies (Fig. 51.4) [25]. Several studies investigating the impact of thrombolysis and thrombectomy show significantly worse outcomes measure by the Modified Rankin Score between DM and non-DM groups. However, this association has not been found in several other reperfusion studies, and therefore, patients with DM and acute ischemic stroke should receive reperfusion therapy, in particular thrombolysis within a 3 h time window. Although current standards of care, indicated by the 2019 AHA (American Heart Association) guidelines, do not recommend intravenous thrombolysis treatment for patients within a 3–4.5 h time window with a history of concurrent DM and prior stroke, further large-scale studies on the relationship between DM and prior stroke properly determine its use in this population [26].

In spite that hyperglycemia is present in approximately 40% of patients with acute ischemic stroke and is associated with worse clinical outcomes, the efficacy of intensive treatment of hyperglycemia in this setting has been disappointed. Current acute stroke guidelines from the American Stroke Association suggest treating hyperglycemia to achieve a blood glucose level in the range of 140–180 mg/dL (7.8–10.0 mmol/L) and close monitoring to prevent hypoglycemia [26]. The Stroke Hyperglycemia Insulin Network Effort (SHINE) randomized clinical trial was conducted to assess the efficacy of intensive versus standard blood glucose control in 1151 patients with hyperglycemic acute ischemic stroke who received either intensive treatment of hyperglycemia (target blood glucose concentration of 80–130 mg/dL) or standard treatment of hyperglycemia (target glucose concentration of 80–179 mg/dL). Intensive compared with standard glucose control did not improve 90-day functional outcomes

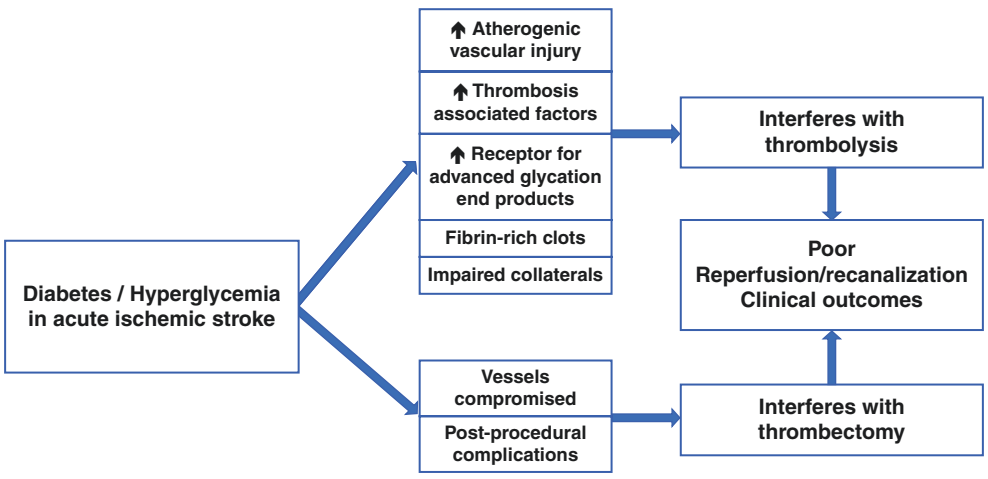

Fig. 51.4 Reperfusion outcomes in patients with diabetes and acute ischemic stroke presenting with acute hyperglycemia. Diabetes and acute hyperglycemia are likely to be associated with poor reperfusion and recanalization outcomes in patients with acute ischemic stroke, due to several factors including vascular injury, clot composition, and impaired collaterals; and then, hyperglycemia appears to interfere with the efficacy of reperfusion therapies (thrombolysis or thrombectomy). (Modified from Fig. 4, [25])

in patients with acute ischemic stroke and hyperglycemia. These findings do not support using intensive glucose control in this setting [27].

On the other hand, though the primary purpose of both parenteral insulin and oral diabetic medications is to prevent hyperglycemia, there is data that suggests that certain classes of these drugs may improve outcomes during the acute phase of an ischemic stroke, through the so-called neuroprotection process. Neuroprotection for stroke defines any strategy directly targeting brain parenchyma with the goal of antagonizing the harmful molecular and cellular events responsible for the ischemic damage thereby allowing brain cells to survive to reduced cerebral blood flow [28, 29]. White et al. noted that in a systematic review of animal studies, the administration of TZDs (thiazolidinediones) during the time of cerebral ischemic injury was associated with improved neurologic outcomes and a decrement in the overall stroke burden [30]. Though these studies have not yet been extrapolated for validity in human subjects, it is noteworthy that rosiglitazone reduced infarct volume regardless of administration before or after induction of ischemia in rat brains [28]. Interestingly, GLP-1 Ras and DPP-IVIs are endowed with a variety of pleiotropic (neuroprotective) properties demonstrated in experimental stroke models, suggesting a possible role in the treatment of acute cerebral ischemia [31]. Considering that they share several neuroprotective effects, an adequate basis exists for explorative clinical investigations on additive GLP-1 agonist plus DPP (dipeptidyl peptidase)-IVI treatment of hyperglycemia in patients with acute ischemic stroke. This strategy would assume that, while GLP-1R agonists directly interact with cerebral receptors, the action of DPP-IVIs is mediated by increasing the effects of GLP-1 including pleiotropic effects. This therapeutic option represents a basically novel strategy to confront hyperglycemia in acute ischemic stroke [31].

Diabetes and Primary Stroke Prevention

Ischemic stroke is a direct complication of diabetes with a complex interplay of multiple risk factors for cerebrovascular disease including hypertension, atherosclerosis, smoking, atrial fibrillation, and a myriad of less well-studied pathophysiological processes of contributors such as obstructive sleep apnea (Table 51.1). Macrovascular complications of hyperglycemia have been less well studied and are more difficult to directly correlate with a specific glucose control target for treatment as has been noted in UKPDS, ACCORD, and ADVANCE trials. Fortunately, microvascular complications as they relate to target HbA1C have been easier to correlate with longitudinal study data, and the cellular pathways by which hyperglycemia affects vascular endothelial cell dysfunction are beginning to be better understood. Primary prevention of ischemic stroke clearly requires hyperglycemic control, but the degree of glycemic control and its effect on other primary stroke risk factors is of equal importance for stroke prevention [32].

A review of the most current literatures reveals that primary stroke prevention is dependent on chronic control of hyperglycemia with a target HbA1C of < 7% as well as the monitoring of both fasting serum glucose and postprandial dysglycemia. What the ACCORD, ADVANCE, and VADT trials helped demonstrate was that all diabetics benefited from a target HbA1C of around 7% regardless of their baseline HbA1C, duration of disease, or baseline comorbidities. More intensive glucose control can lead to increased mortality in some subgroups while in young patients with DM disease duration of less than 15 years may in fact benefit from intensive glucose control with a lower target HbA1C [33].

The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial demonstrated that patients with impaired fasting blood glucose, although not meeting diagnostic criteria for diabetes, were at increased risk of developing DM and subsequently at higher

Table 51.1 AHA/ADA guidelines for primary stroke prevention

Diabetes	Hyperlipidemia	Hypertension	Atrial fibrillation	Other risk factors
BP goal <140/90 mmHg	Statin use for patients with high CV risk	Lifestyle changes and BP screening[a]	Coumadin for CHA_2DS_2-VASc score ≥ 2[b]	Weight reduction if BMI ≥ 25
Statin use for CV risk reduction	Fibric acid derivatives only for elevated triglycerides[c]	Goal BP of <140/90, reduction more important than BP agent used	Nonvalvular AF and CHA_2DS_2-VASc of 0, no anticoagulants	Smoking cessation in all patients
No role for aspirin or fibrates	No role for statin lipid-lowering medications	Self-measurement of BP	Screening for AF in patients 65 or older with exam and EKG	40 min, three days/week moderate exercise

ADA guidelines per the following: Cefulu W et al. "American Diabetes Association: Standards of Medical Care in Diabetes—2015," *The Journal of Clinical and Applied Research and Education: Diabetes Care* 2015; 38 (1): S1–S93

[a]*BP* blood pressure, *CHA2DS2-VASc* congestive heart failure, hypertension, age, diabetes, stroke, and vascular disease, *CV* cardiovascular, *AF* atrial fibrillation, and *BMI* body mass index

[b]In patients with low hemorrhage risk and valvular AF (atrial fibrillation)

[c]No role for fibric acid derivatives in decreasing future stroke risk

risk for ischemic stroke [22]. According to Mi et al., elevated fasting blood glucose was an independent predictor for first-ever ischemic stroke or recurrent stroke [34]. Additionally, it has been surmised for years that prediabetic or diabetic patients who experience repeated episodes of dysglycemia are at higher risk of cerebrovascular disease and dysfunction of the neurovascular endothelium [35]. However, data from trials to date such as NAVIGATOR are conflicting, and it is not currently understood how to best reduce cardiovascular risks in patients with impaired fasting blood glucose or postprandial glucose [36]. What has been better studied is the impact that various antidiabetic drug classes have on benefiting patients in primary stroke prevention.

Influence of Antidiabetic Drug Classes for Primary Stroke Prevention

Though DMI patients typically use forms of synthetic insulin for glycemic control, it is well known that DMII diabetics have a wide range of oral medications available for the treatment of hyperglycemia. These diabetic drugs (Table 51.2) include multiple medications with varying mechanisms of action and benefit for treating hyperglycemia as it pertains to primary stroke prevention. In addition to reviewing these medications by drug class, it is also important to address the use of these medications around the time of an ischemic stroke as some antihyperglycemics such as thiazolidinediones can potentially improve patient outcomes [30].

The use of parenteral insulin is the most obvious and well-studied mechanism to control hyperglycemia in DMI patients. In DMI and DMII patients self-administering glargine or NPH compared to basal insulin peglispro, there has been no reported clinically significant difference in preventing future ischemic strokes or CV events. There has been associated cardiovascular benefit with insulin use and improvement of comorbid stroke risk factors outside of the documented physiologic benefits of achieving normoglycemia. Interestingly, prior studies in type 2 diabetes mellitus patients have noted that long-acting insulin formulations may be implicated in exacerbating CAD leading to increased risk of myocardial infarcts [37]. A cross-sectional, international cohort study performed by Al-Rubeaan et al. as well as studies derived by data from the Hong Kong Diabetes Registry noted clinically significant elevation in stroke risk for patients using insulin for control of hyperglycemia [38]. However, this associated stroke risk was possibly due to the fact that type 2 DM patients who are parenteral insulin users

Table 51.2 Diabetic drug classes and primary stroke prevention

Hyperglycemic medication	Mechanism of action	Stroke risk factors	Side effects	Supporting studies	Important findings
IV insulin (glargine, NPH)	Serum glucose absorption	Hyperglycemia, CAD	Hypoglycemia	UKPDS	Macrovascular outcomes similar to oral antihyperglycemics
Biguanides (metformin)	Decreased hepatic gluconeogenesis	HLD, CAD, HTN	Hypoglycemia Weight gain	UKPDS Gejl et al.	Improved outcomes in the obese
Sulfonylureas (glipizide, glyburide)	Pancreatic secretagogue	Hyperglycemia[a]	Cardiac deaths	UKPDS Azimova et al.	↓ mortality in DM patients
Meglitinides (nateglinide)	Pancreatic Secretagogue	Hyperglycemia	Hyperglycemia	NAVIGATOR Azimova et al.	No improvement in CV outcomes in IGT/DM patients
DDP-4 inhibitors (sitagliptin)	Inhibit incretin, GLP-1, GIP degradation[b]	Postprandial hyperglycemia	CKD (rare)	Azimova et al. Fisman et al. Enders et al.	↓ risk of CV outcomes Rate of MI or stroke in DM patients unchanged
Glucosidase inhibitors (acarbose)	Intestinal α-glucosidase inhibitor	Postprandial hyperglycemia HTN	GI side effects, hepatotoxicity (rare)	STOP-NIDDM	Acarbose can prevent conversion of IGT patients to DM status
Thiazolidinediones (pioglitazone)	PPAR activators	HTN	HLD CAD exacerbation	Azimova et al. White et al.	Pioglitazone ↓ risk for macrovascular events in high-risk patients
GLP-1 (exenatide, liraglutide)	Inhibits glucagon Insulin secretagogue	Weight loss, HTN, and HLD	GI side effects	Azimova et al. Mearns et al.	20% ↓ risk of CVD in DM II patients
SGL2 inhibitors (gliflozins)	Sodium glucose cotransporter inhibitor	HTN, HLD, and weight loss	AKI and CKD	Mearns et al.	Reduces SBP ↑ weight loss
Bile acid sequestrant (colesevelam)	Binds intestinal bile acids	HLD and CAD	None	Ganda et al. Porez et al.	↓ future CV events

[a]Did not reach significance for macrovascular outcomes

[b]*GLP-1* glucagon-like peptide 1 receptor, *GIP* glucose-dependent insulinotropic peptide, *DDP-4* dipeptidyl peptidase-4 inhibitors, *GLP-1* glucagon-like peptide 1, *SGL2* sodium glucose cotransporter, *GIP* gastric inhibitory polypeptide, *PPAR* peroxisome proliferator-activated receptors, *CAD* cardiac arterial disease, *HLD* hyperlipidemia, *HTN* hypertension, *CKD* chronic kidney disease, *AKI* acute kidney disease, *GI* gastrointestinal, *DM* diabetes mellitus, *CV* cerebrovascular, *IGT* impaired glucose tolerance, *MI* myocardial infarct, and *SBP* systolic blood pressure

have poorly controlled hyperglycemia [38]. Treating hyperglycemia with oral agents in DMII patients is more complex than just parenteral insulin formulations; however, many options exist for treating this patient population.

Biguanides such as metformin are a class of oral antihyperglycemics currently available for treating DMII. Metformin was used in the UKPDS trial and demonstrated a 32% relative risk reduction of cardiac ischemia and ischemic stroke in diabetics as well as 42% reduction in all macrovascular deaths related to diabetes. Interestingly, the combination of metformin and injected insulin in the same study demonstrated a significantly decreased risk for the development of macrovascular disease including ischemic stroke when patients were followed for over four years after completion of the study [39]. These data are significant in so far as that it has been documented that newly diagnosed DMII patients have a 10% increased absolute risk of stroke within five years of initial diagnosis [40]. Treatment of DMII with metformin not only decreases the increased absolute risk of ischemic stroke but also may help treat comorbid risk factors such as hypertension and hyperlipidemia, thereby further decreasing the risk of future ischemic stroke (Table 51.1) [39].

According to Gejl et al., the biguanide drug class may affect multiple stroke risk factors such as hyperglycemia and hyperlipidemia yielding a decrease in the occurrence of major cardiac or cerebral ischemic events [41]. Similarly, in large retrospective cohort studies comparing diabetics treated with metformin and diabetics treated with antihyperglycemics not including metformin, there was a significantly lower risk of stroke with an adjusted hazard ratio of 47 in the metformin group [39]. Metformin's mechanism of action in reducing cholesterol levels is not completely understood but may involve decreasing hepatic secretion of lipoproteins resulting in lower VLDL, plasma triglycerides, and LDL/HDL ratio. The cardioprotective effects of metformin in animal studies have also been well documented, and it is likely that diabetics who have an MI while on metformin have a reduction in both MI size and burden of reperfusion injury [42]. The mechanism by which metformin decreases hypertension in the diabetic is less well understood.

Sulfonylureas such as glipizide and glyburide have been long used to treat DMII, but a large body of evidence has provided conflicting data on this drug class's cardiac profile especially in patients with pre-existing CAD [39]. Per data in the UKPDS trials, intensive treatment of DMII patients with sulfonylurea monotherapy led to a significant decrease in microvascular complications though the decrease in macrovascular complications such as ischemic stroke did not reach significance [10]. Sulfonylureas likely carry an increased risk of cardiovascular complications and are still not considered a first-line monotherapy drug for any DMII patient that has concomitant underlying CAD [39].

Though meglitinides, such as repaglinide and nateglinide, are short-acting glucose-lowering drugs that do not affect lipid levels, they do lower HbA1C levels and manage hyperglycemia [39]. In prediabetics or patients with IGT, nateglinide was associated with a significant increase in episodes of hyperglycemia and unfortunately was unable to reduce the incidence of patients suffering cardiovascular or cerebrovascular ischemic events. Interestingly, it was noted that prediabetics who used nateglinide compared to placebo were not at lower risk of developing diabetes over the median five-year period of longitudinal analysis [43]. Conflicting data also exist on repaglinide's ability to decrease stroke risk in diabetics. While repaglinide did demonstrate similar efficacy in controlling hyperglycemia, metformin is more effective in decreasing the risk of CVD in DMII patients [39]. Whether meglitinides are associated with increased cardiovascular risk is not known; however, since their mode of action is similar to sulfonylureas, the same concern exists.

Dipeptidyl peptidase 4 (DDP-4) inhibitors are diabetic medications such as sitagliptin, linagliptin, alogliptin, and saxagliptin, which prolong the bioavailability of incretins, thereby better controlling postprandial hyperglycemia. Along with the regulation of postprandial glucose, these medications have been associated with decreasing vascular endothelial inflammation and improvement of endothelial dysfunction existing in diabetic vasculature as discussed earlier [39]. Gliptin-induced changes including a decrease in serum lipid levels and hypertension were also noted in animal studies [44]. However, according to Enders et al., diabetics taking DDP-4 inhibitors in combination with metformin when compared to patients taking metformin and sulfonylureas did not experience significantly reduced risk of future ischemic stroke [45]. Linagliptin was associated with a noninferior risk of a composite CV outcome in the CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus) study [46]. Regarding CV safety of DPP-4 inhibitors (especially for heart failure), a recent meta-analysis by Mannucci et al. demonstrated a safe cardiovascular profile as its use was not associated with any major cardiovascular events [47].

Acarbose, an alpha-glucosidase inhibitor (AGI), serves a similar role in glycemic control as DDP-4 inhibitors in that they reduce postprandial hyperglycemia. Though its complete cardiovascular safety profile is not known, data from the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial reflects a positive effect of AGIs in the management of comorbid stroke risk factors with patients experiencing a hypertension relative risk reduction of 34%. STOP-NIDDM also demonstrated a nearly 50% relative risk reduction in cardiovascular events for patients taking acarbose though a head-to-head comparison study with metformin has yet to be performed [39].

Pioglitazone and rosiglitazone improve the utilization of available serum glucose and decrease the pro-inflammatory state of vascular endothelium in diabetics [39]. These two medications belong to a drug class known as thiazolidinediones. Their ability to help mitigate the oxidative injury from ROS in vascular endothelium may contribute to an overall decrease in future stroke risk in diabetics [24]. However, stroke risk in patients who take rosiglitazone remains uncertain as previous studies have implicated this medication with worsening hyperlipidemia, thereby potentially putting diabetics at increased risk of ischemic stroke. Data is conflicting concerning TZDs, especially rosiglitazone, and their role in risk development or worsening of baseline cardiac disease in diabetics. The thiazolidinediones are not recommended for use in patients with diabetes and concomitant severe congestive heart failure or prior CAD [39].

Glucagon-like peptide 1 agonists are oral antihyperglycemics with a mechanism of action similar to DDP-4 inhibitors in that they work on incretin deficiencies inherited to the pathophysiology of DMII. The GLP-1 agonists including exenatide, liraglutide, dulaglutide, albiglutide, lixisenatide, and semaglutide have been shown to significantly decrease overall HbA1C in diabetics. Additionally, the use of GLP-1 agonists in overweight diabetic patient populations has resulted in significant weight loss greater than five pounds resulting in subsequently improved control of stroke risk factors including hyperlipidemia and hypertension [48]. This class of antihyperglycemics has also been associated with cardiovascular protective effect, regulation of postprandial hyperlipidemia, and improvement of fasting LDL [39]. Recent trials (REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) with dulaglutide, HARMONY with albiglutide, LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Result) with liraglutide, SUSTAIN-6 (Trial to Evaluate Cardiovascular Other Long-term Outcomes with Semaglutide) with semaglutide, and EXSCEL (Exenatide Study of Cardiovascular Event Lowering Trial) with exenatide) have shown potential for GLP-1 receptor agonists in reducing cardiovascular events, including stroke [49–53]. In particular, a main reduction of stroke rate was observed for semaglutide, the oral and parenteral preparations associated with 26% and 39% reductions, and dulaglutide, associated with 24% reduction in stroke [54]; moreover, a recent systematic review with meta-analysis by Bellastella et al. regarding GLP-1RA trials involving 56,004 participants demonstrated a significant 16% reduction in stroke rates [55].

Other oral antihyperglycemics like sodium glucose cotransporter-2 (SGLT2) have similar efficacy to other oral diabetic medications in controlling HbA1C. SGLT2s are superior to sulfonylureas in improving hypertension and as a class are associated with significant weight loss in diabetics similar to GLP-1 agonists. Compared to placebo, SGLT2s have not been implicated in hypoglycemic events among diabetics though it should be noted that a majority of the data known about their efficacy and management of hyperglycemia comes from data in which patients used them concomitantly with metformin. Data suggest that SGLT2s, when compared to placebo, have clinically significant beneficial effects on controlling major stroke risk factors including hyperlipidemia and hypertension [48]. A recent 2021 meta-analysis by Tsai et al., of five trials, including CREDENCE and CANVAS trials with canagliflozin, VERTIS CV with ertugliflozin, DECLARE-TIMI 58 with dapagliflozin, and EMPA-REG OUTCOME with empagliflozin, involving 46,969 participants showed no significant or neutral effect of SGLT2 inhibitors on the risk of stroke in DM patients [56]. In subgroup analyses, no significant effects of SGLT2 inhibitors were observed against fatal stroke, nonfatal stroke, ischemic stroke, or TIA (transient ischemic attack). However, it was found a significant 50% reduction in hemorrhagic stroke, indicating a potential protective role of SGLT2 inhibitors against hemorrhagic stroke [56]. This could be of great importance because hemorrhagic stroke is the worst stroke type.

In terms of combination therapy for control of hyperglycemia in DMII patients, bile acid sequestrants such as colesevelam have also shown to be beneficial in improving glycemic control. Clinically significant reductions in LDL have been observed with colesevelam use especially when combined with statin [57]. Bile acid sequestrants regulate multiple pathways of lipid synthesis and also appear to have an anti-inflammatory effect on endothelial cells. Some retrospective studies have noted a stroke risk reduction of 43% in patients adherent to taking colesevelam with baseline hyperlipidemia and diabetes though this relatively large risk reduction may have been skewed by confounding variables [39]. Mitigating the deleterious effects of hyperlipidemia, bile acid sequestrants have the potential to reduce the incidence of future ischemic stroke as well as cardiovascular disease [58].

Optimization of Diabetic Control and Additional Stroke Risk Factors

American Heart Association (AHA) guidelines for the primary prevention in stroke in diabetics recommend that all patients with an elevated ten-year stroke risk, which includes all diabetics, benefit from treatment with a statin [32]. Even in diabetics without comorbid cardiovascular disease, the risk of stroke is significantly elevated in patients with uncontrolled LDL compared to diabetics with LDL ≧100 mg/dL [59] with a 24% reduction in ischemic stroke occurrence associated with statin use quoted in prior studies. It is impor-

tant to note that though increased LDL levels have a direct association with increased risk of ischemic stroke, there is no associated stroke risk for diabetics with elevated total cholesterol and increased HDL [32]. Trials such as the Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) demonstrated that stroke risk is significantly decreased with statin administration even in healthy individuals devoid of increased risk for ischemic stroke [60]. The regulation of atherosclerosis and hyperglycemia is intricately related to an interrelated, complex pathophysiology as discussed earlier in this chapter.

According to current AHA guidelines and based on data derived from the UKPDS trial, it is recommended that aggressive blood pressure management should occur in all patients with DM. The UKPDS trial demonstrated that a goal blood pressure of 140/90 is associated with a 44% relative risk reduction of future ischemic stroke in patients with either DMI or DMII [32]. Which medication regimen to use for achievement of goal blood pressure in patients with DM and baseline increased CAD risk is a point of contention as conflicting data exist as to what constitutes best medical management. Nevertheless, DM patients without additional CAD risk factors at baseline have been consistently found to have an elevated risk of future stroke due to poorly controlled hypertension alone despite AHA recommendations [59]. Per Meschia et al., prior studies such as HOPE found that ramipril administration in diabetics with CAD risk factors resulted in a significant decrease in the relative risk of future ischemic stroke (25% RR, 95% CI: 12–36, $p = 0.0004$) as well as a significant reduction in cardiovascular-related death [32]. Other studies including the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) found that a blood pressure regimen consisting of both amlodipine and perindopril resulted in a 25% risk reduction in future strokes though more recent studies considered that successful reduction of BP is more important in reducing stroke risk than the choice of a specific agent, and treatment should be individualized on the basis of other patient characteristics and medication tolerance [32].

In the ADVANCE trial, ACE inhibitor use with concomitant indapamide administration did not result in a significant decrease in future stroke risk for DMII patients [32]. Similarly, in the diabetic subset of patients studied in the Avoiding Cardiovascular Events Through COMbination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, it was found that an ACE inhibitor plus diuretic or calcium channel blocker did not result in decreased stroke risk over the three-year follow-up period [32]. Administration of ARBs (angiotensin receptor blockers) such as valsartan has also been investigated for their ability to decrease future stroke risk in diabetics. The NAVIGATOR (Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research) trial, which compared valsartan to placebo, demonstrated that patients with IGT and increased baseline risk for CAD did not have a significant decrease in future stroke risk [43]. Trials such as GEMINI (Genomic Medicine for III Neonates and Infants) suggest that β-blockers like carvedilol are effective and safe to use in diabetic patients to reduce blood pressures to goal. However, there have not been substantial investigations into the role of β-blockers and future stroke risk reduction in diabetics leaving this as a gap of knowledge within the literature [61].

Inflammatory changes induced by hyperglycemic states of DM patients have been shown to induce pathophysiologic changes conductive to the development of atrial fibrillation (afib). In fact, it is a commonly accepted knowledge that DM is a risk factor for the development of afib [62]. It is also known that patients with atrial fibrillation (afib) have a substantially elevated risk of ischemic stroke with diabetics at even higher risk based on the $CHADS_2$ score [32]. According to Dublin et al., treated diabetics have a 3% annual risk of developing afib that is additive based on the duration of diagnosed diabetic state [44]. A 14.9% incidence of afib exists within the diabetic population, and the incidence is nearly six times higher than that of the general population [63].

The recommendations for risk reduction of afib in diabetics are multifaceted. Depending on the $CHADS_2$ or CHADS-VASC score, patients with both DM and afib will carry at least a moderate risk of future cardioembolic, ischemic stroke [32]. As noted earlier during the discussion on diabetes and microvascular complications, the risk of peripheral arterial disease, hypertension, and aortic plaque development is elevated in all diabetics as well as those with IGT. Studies have shown that pathophysiologic changes similar to those that cause endothelial dysfunction in diabetics can also cause autonomic dysregulation which increases the risk for afib. Once these changes occur, it is important to decrease the risk of future ischemic stroke by either starting anticoagulation therapy in moderate- to high-risk patients, rate/rhythm control, or catheter ablation [64]. Unfortunately, DM patients often have neuropathy and may be unaware that they have afib, thereby making catheter ablation a less viable option due to higher rates of cardioversion failure [63]. Therefore, proper management of hyperglycemia is required to prevent changes on the cellular level that place DM patients at higher risk for the development of another ischemic stroke risk factor.

Some studies exist which have assessed whether specific oral antihyperglycemics such as metformin decrease future risk for DM to develop afib. A prospective cohort with 5.4-year median follow-up was performed by Chang et al. who noted that DM patients taking metformin had a significantly lower risk for developing afib than did DM patients not taking metformin [62]. The mechanism of benefit suggested is that metformin may reduce hyperglycemia-induced inflammatory

injury to atrial myocyte, thereby preventing tachyarrhythmias known to lead to afib [62]. Moreover, it has been established that there are both increased plasma viscosity and increased activation of thrombocytes in DM patients leading to further risk of clot formation in individuals already prone to developing afib [65]. In summary, DM in patients with AF is associated with increased cardiovascular and cerebrovascular mortality. DM is a known risk factor for thromboembolic events in patients with AF and is associated with a 70% relative increase in risk of stroke [66]. The pathophysiology of diabetes-related AF is not fully understood but is related to structural, electromechanical, and autonomic remodeling. For patients with diabetes and CHA2DS2-VASc scores ≥2, direct oral anticoagulants may be recommended over warfarin, in spite that the relative safety and efficacy of direct oral anticoagulants versus warfarin were similar regardless of diabetes status [67]. Moreover, patients with longer duration of diabetes or insulin-requiring diabetes may benefit more from oral anticoagulation, even in the absence of other major risk factors included in the CHA2DS2-VASc score [66].

Directly smoking tobacco products and second-hand smoke exposure put patients at increased risk for ischemic stroke and increase progression of diseases such as hypertension and atherosclerosis [32]. Nondiabetic smokers have twice the risk of suffering a future ischemic stroke [61] while DM patients who are active smokers carry a 50% higher risk for all-cause mortality and stroke based on data derived from a large meta-analysis [68]. It is likely that smoking acutely causes hypercoagulable states within the atherosclerotic vasculature and over time causes increased rates of atherosclerotic changes within intracranial and extracranial arteries [32]. AHA recommendations for smoking cessation treatment are similar to those made by O'Keefe et al. and include counseling in combination with medications such as varenicline, clonidine, bupropion, and nicotine supplementations [61]. The differences in future stroke risk for smokers who are diabetics versus nondiabetics have not been well delineated.

A risk factor for stroke that is now becoming more recognized is abdominal adiposity more so than patient BMI. However, it should be noted that no current studies have definitively associated increased future stroke risk with increased abdominal adiposity independent of associated comorbidities such as hypertension, DM, and smoking. Olofindayo et al. conducted a prospective cohort study which found that in patients who were both obese and diabetic, the risk for future ischemic stroke was 73% higher than in age-matched individuals with only DM or central obesity alone [69]. It has also been found that regardless of diabetic status, a patient's future stroke risk nearly triples in the setting of obesity with current 2014 AHA guidelines recommending weight loss in patients with BMI ≥25 to prevent future ischemic stroke [32].

According to O'Keefe et al., waist size has proven to be an independent risk factor for the development of DM [61]. Obesity, regardless of adipocyte corporal distribution, has also been linked to the development of tachyarrhythmias with some studies noting a 4.7% increased risk of afib per increase of each unit of 1 kg/m^2 in BMI [65]. It is also well known that a large percentage of patients with DMII or IGT are overweight or obese placing a large percentage of DM patients overall at increased risk of future ischemic events based on BMI and waist circumference alone. Class 1 level B evidence suggests that modification of lifestyle is necessary for DM patients in order to decrease the risk of ischemic stroke with higher-level evidence denoting a clear correlation with weight loss and achieving normotension [32].

DM patients who demonstrate central adiposity and insulin resistance often have metabolic syndrome [21] though other characteristics of the syndrome including IGT (fasting serum glucose ≥ 110 mg/dL), hyperlipidemia, and hypertension can also be present [32]. Metabolic syndrome is associated with increased risk of ischemic stroke due to the presence of the risk factors which define it rather than by the existence of the syndrome itself [34]. 2014 AHA guidelines currently recognize that up to 38.5% of the general US population meets criteria for metabolic syndrome. Data from large retrospective studies have demonstrated an increased prevalence of metabolic syndrome (43.5%) in patients with a history of ischemic stroke though no direct correlation between metabolic syndrome and increased risk of stroke has been found. Additionally, prospective trials such as Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) did not find an increased risk for future stroke in the subset of 642 patients with both metabolic syndrome and prior stroke. Currently, the guidelines for primary prevention of stroke as they pertain to metabolic syndrome are that patients should focus on the management of the individual risk factors that define the disease via weight loss and proper medication regimens [32].

Other less studied risk factors such as DM and ischemic stroke include obstructive sleep apnea (OSA). OSA is not only a risk factor for future ischemic stroke but also has been suggested to have a significant association with the development of DMII. Not surprisingly, obese diabetic patients are at higher risk for developing OSA though obesity itself is an independent risk factor for OSA with some studies quoting prevalence as high as 27% in patients with BMI ≥ 30 [70]. Per Kent et al., a recent prospective cohort comprised of nearly a thousand patients found that patients with moderate to severe OSA were about three times more likely to develop DMII within an average of 2.7 years compared to non-OSA participants [71]. Other larger cohort studies with an average follow-up of nearly five years demonstrated similar results establishing a clear clinical correlation between OSA and DMII [71].

The Wisconsin Sleep Cohort Study and the Sleep Heart Health Study both demonstrated increased stroke risk in patients with OSA. The Wisconsin study was comprised of a prospective cohort which demonstrated that severe OSA conferred a triple risk for future ischemic stroke (OR, 3.09, 95% of CI: 0.74–12.81) [72]. The Sleep Heart Health Study found that when adjusting for all confounding risk factors, there was still a linear positive correlation between rising apnea-hypopnea index (AHI) and risk of stroke [73]. There have been few randomized trials to test the efficacy of OSA treatment as it relates to primary prevention of ischemic stroke though a recent study by McEvoy et al. did note that CPAP treatment versus sham treatment in patients with moderate to severe OSA and concomitant CAD/cerebrovascular disease did not result in a significant difference in cardiovascular-related deaths including stroke ($p = 0.34$; HR, 1.1; CI, 0.91–1.32) [74]. Currently, screening based on symptoms such as daytime sleepiness, snoring, and clinical suspicion is recommended [32]. However, the link between OSA and primary stroke prevention is becoming more and more clinically relevant with up to 4% of the US population now having a form of sleep apnea [32]. The final risk factor for primary stroke prevention that will be discussed is physical inactivity.

Moderate- to high-intensity physical activity has been shown to decrease risk for future cardiovascular events in patients with diabetes independent of any concomitant stroke risk factors including HLD (hyperlipidemia), HTN (hypertension), obesity, and smoking [33]. However, in the general population, some studies report that baseline low physical activity level is not associated with increased rates of future stroke when adjusting for confounding stroke risk factors [75]. Conversely, based on more recent meta-analysis derived data, the current AHA guidelines indicate that active men and women have a 30% lower annual risk of stroke than their inactive counterparts. The degree of intensity, duration, and frequency needed to achieve maximal protective effect from the development of future stroke is a point of debate. Overall, the current recommendation is for 40 min of moderate to intense, aerobic exercise at least three days per week. The data for current recommendations are derived from observational studies as clinical trials delineating clear risk reduction have not been performed [32].

Diabetes and Secondary Stroke Prevention

DM and prediabetes are present in around 30% of patients with acute ischemic stroke and are associated with increased risk for stroke recurrence [76]. Up to 95% of patient with diabetes mellitus are type II with hyperglycemia preceding DM diagnostic criteria in the form of impaired fasting glucose, impaired glucose tolerance (IGT), and episodic hyperglycemia. Wu et al. conducted a prospective cohort study which found that after initial stroke, prediabetic patients with HbA1c $\geq$ 6.1% had a 61.3% recurrent stroke risk at three months that was still elevated at 51.1% after a year [77]. This was a significant finding due to the traditional threshold for HbA1c of 6.5% being diagnostic for DM, but in lieu of the previously discussed initial stroke risk conferred to patients that only have IGT, this is less surprising. Duration of DM diagnosis at the time of initial stroke may play a role in determining the level of glucose control needed to help prevent future strokes. According to Wu et al., patients with a long-standing history of DM did not benefit from intensive glycemic control as it relates to secondary stroke prevention [77]. However, this contrasted with the benefit found in newly diagnosed DM patients with a history of stroke who were noted to have decreased recurrent stroke risk with a goal of near normoglycemia [77].

It remains a fact that DM is highly prevalent in the global population and places patients within all age demographics at risk for poor outcomes after an initial stroke. In fact, DM is an independent predictor for both primary lacunar strokes as well as for poor prognosis for recurrent ischemic cerebrovascular events [78]. Even young adults <50 years of age with a history of DMI had a high incidence of recurrent ischemic stroke independent of concomitant risk factors [79]. Recently, in a large, cross-sectional multicenter study of DMII patients, it was noted that in the setting of poststroke recovery, only about 60% of patients achieved an HbA1c of $\leq$7.5%. Persistently, elevated HbA1c values are concerning in terms of hyperglycemia's influence on microvascular outcomes though the relativity to recurrent stroke in DM patients was again indeterminate [80].

Rigorous measures of secondary prevention are of paramount importance to avoid stroke recurrence in patients with diabetes. The main messages of the recently published AHA guidelines for secondary stroke prevention in patients with an ischemic stroke or TIA who also have diabetes include the following [76]:

- The goal for glycemic control should be individually based, and for most patients, achieving a goal of HbA1c $\leq$7% is recommended.
- Treatment of diabetes should include glucose-lowering agents with proven cardiovascular benefit to reduce the risk for future major adverse cardiovascular events (i.e., stroke, MI, cardiovascular death). As has been previously discussed, recent clinical trials [54–56] demonstrated that at least one drug in each of the three classes of glucose-lowering medications can reduce the risk for major adverse cardiovascular events in patients with DM and established atherosclerotic vascular disease, including ischemic stroke or high risk: thiazolidinediones, glucagon-like protein 1 (GLP-1) receptor agonist, and sodium glucose cotransporter 2 inhibitor.

- Considering the limited number of therapies available for prevention and treatment of stroke and the substantial attendant disability and impact on patients and their families, recent data meaningfully supports the consideration of GLP-1 receptor agonists for stroke prevention in people with type 2 diabetes at increased cardiovascular risk [54]. In patients with established atherosclerotic cardiovascular disease, including ischemic stroke, when prevention of further vascular events is the priority, GLP-1 receptor agonist therapy should be added to metformin independently of baseline HbA1c [76, 81].
- Multidimensional care (i.e., lifestyle counseling, medical nutritional therapy, diabetes self-management education and support) is indicated to achieve glycemic goals and to improve other stroke risk factors.

Around 50% of patients without diabetes with ischemic stroke have insulin resistance. Both conditions have been associated with increased risk for first ischemic stroke. The Insulin Resistance Intervention after Stroke (IRIS) trial found that insulin-resistant patients with prior stroke receiving had a 2.8% risk reduction for future stroke compared to insulin-resistant patients randomized to placebo.

Pioglitazone reduced the risk of recurrent stroke or MI by 24% (RR, 0.76 [95% CI, 0.62–0.93]), from 11.8% among placebo versus 9.0% among pioglitazone [82]. However, active treatment was associated with adverse events like weight gain and increased bone fracture risk that have restrained clinical use of pioglitazone. To date, the IRIS trial is one of the few studies to evaluate insulin-resistant patients by treatment with hypoglycemic medications with a primary endpoint of recurrent stroke or MI.

The metformin and sitagliptin in patients with impaired glucose tolerance and a recent TIA and minor ischemic stroke (MAAS) trial was aimed to assess the feasibility, safety, and effects on glucose metabolism of metformin or sitagliptin in these patients. Results revealed that metformin and sitagliptin were both effective in reducing fasting glucose and HbA1c levels in patients with recent TIA or minor ischemic stroke and IGT. However, the reduction of glucose levels and sample size was relatively small precluding any clinical relevance. A phase III trial is needed to investigate whether medical treatment, compared with lifestyle intervention, not only improves glucose metabolism in IGT but also leads to reduction of recurrent TIA or ischemic stroke in these patients [83].

Management of Additional Risk Factors and Secondary Stroke Prevention in DM

The final part of this chapter will focus on the additional secondary stroke risk factors as they relate to recurrent stroke prevention. Clearly delineated recommendations have been made for the management of recurrent stroke risk factors including hypertension, hyperlipidemia, and atrial fibrillation, among others (Table 51.3).

Hypertension is one of the most important modifiable risk factors to regulate in order to prevent the recurrence of ischemic stroke. Studies including the Post-stroke Antihypertensive Treatment Study (PATS) and Perindopril Protection Against Recurrent Stroke (PROGRESS) both noted lower rates of recurrent strokes when patients randomized to antihypertensive treatment achieved systolic blood pressures of 140 mmHg. The PROGRESS trial found that further recurrent stroke risk reduction was achieved with systolic blood pressure < 140 mmHg. Confirmation of the importance of antihypertensive administration with goal titration to blood pressures of 140/90 mmHg was found via meta-analysis of poststroke individuals though at this time there is no recommendation of specific medication regimen to achieve [76]. Of note β-blockers and diuretics have both been associated with worsening of glucose control in DM patients. A meta-analysis revealed that β-blockers not only increase fasting blood glucose (0.64 mmol) but also raise HbA1C by 0.75% in patients with DM [84]. The same study

Table 51.3 AHA/ADA guidelines for secondary stroke prevention

Diabetes	Hyperlipidemia	Hypertension	Atrial fibrillation	Other risk factors
DM testing after initial stroke	Statin for patients with stroke and LDL ≥ 100[a]	Treat HTN if patient BP ≥ 140/90 mmHg	Antithrombotic for nonvalvular afib	ASA for all ischemic stroke patients
Goal HbA1c ≤6.5% per AHA Goal HbA1c ≤7% per ADA[b]	Goal LDL < 100 mg/dL	Goal BP of ≤140/90 mmHg	Aspirin for stroke patients unable to take anticoagulants	Smoking cessation recommended for all patients
Moderate-intensity treatment for stroke prevention	Dietary and lifestyle recommended	Diet, exercise, and decreased salt intake recommended	Can delay anticoagulants for two weeks if high bleeding risk present	40 min, three days/week moderate exercise

Stroke reduction with statin use in patients with TIA or ischemic stroke of atherosclerotic etiology, high-intensity statin unless patient's age ≥ 75

[a]Treat hypertension (HTN) if BP over 140/90 mmHg for the first few days after stroke

[b]ADA guidelines differ from AHA secondary stroke prevention HbA1c goals with less stringent glycemic control recommended based on data from the ACCORD study

by Hirst et al. also demonstrated that diuretics also raised fasting blood glucose by 0.77 mmol but did not have a significant effect on HbA1C [84]. These drugs and their role as antihypertensives in patients with IGT should be taken on a case-by-case basis.

Up to 87% of both primary and recurrent strokes are ischemic. When there is regulation of both hypertension and atherosclerosis, a significant mitigation in recurrent stroke risk has been observed [67]. In accordance with findings from the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study, it is advised that all individuals be placed on high-dose statin. Results of the SPARCL study showed that there was an absolute risk reduction of 3.5% (p = 0.002) for major cardiovascular events in patients receiving high-dose statin over a five-year follow-up period. In terms of preventing recurrent stroke, patients receiving atorvastatin 80 mg daily were noted having an absolute risk reduction of 2.2% (p = 0.03) without significant side effects. Guidelines for secondary stroke prevention set the benchmark for lipid control with a goal LDL of ≤100 [76, 85]. Of note in a post hoc exploratory analysis of SPARCL, there was found to be a 28% relative risk reduction of recurrent stroke with an LDL of <70 mg/dL without increased risk for intracerebral hemorrhage. There was also a 35% risk reduction for ischemic stroke if at least a 50% reduction in LDL is achieved [86]. Considering the results of the Treat Stroke to Target study, in patients with ischemic stroke or TIA and atherosclerotic disease (intracranial, carotid, aortic, or coronary), lipid-lowering therapy with a statin and also ezetimibe, if needed, to a goal LDL-C of <70 mg/dL is recommended to reduce the risk of major cardiovascular events [76, 87].

In patients with DM, the management of hyperlipidemia is similar as regards to goal LDL, but data from randomized control trials have shown statin benefit for all DM patients at increased risk for cerebrovascular disease [76, 86]. However, the use of statins in DM patients is not without elevated risk for hyperglycemia. Macedo et al. conducted a meta-analysis of the available literature to ascertain the statins may pose a risk of DM development [88]. It was shown that there is a slightly increased risk of developing DM in patients who use statins for at least three years though the odds ratio was low (OR, 1.31; 95% CI, 0.99–1.73) and the number need to harm was 44 patients for a new diagnosis of DM. Other studies produced contrasting results with no association found between statin and DM risk though many of them were of low quality [88].

The annual risk for recurrent stroke in all patients with untreated afib who have had a recent TIA or ischemic stroke is between 7 and 10%. Anticoagulation is the optimal choice for recurrent stroke prevention regardless of diabetic status. In patients with stroke or TIA in the setting of nonvalvular AF who have anticoagulation contraindications, it may be reasonable to consider percutaneous closure of the left atrial appendage with the Watchman device to reduce recurrent stroke and bleeding [76]. The AHA/ADA recommendations for choice of anticoagulant is case dependent, and the timing to prevent recurrent stroke in the patient with afib is no different in DM patients compared to the nondiabetic patient population; however, direct oral anticoagulants may be recommended over warfarin in patients who are unable to maintain a therapeutic INR level with vitamin K antagonist anticoagulants [76]. Other risk factors for recurrent stroke prevention in diabetics include metabolic syndrome and smoking.

Patients with metabolic syndrome may not be at increased risk of recurrent stroke from the syndrome itself, but elevated fasting blood glucose does put DM patients at risk for recurrent stroke [34]. Known risk factors for both recurrent stroke and metabolic syndrome such as HLD, HTN, and DM should be modified to prevent future strokes, but screening for metabolic syndrome is not recommended. Limited data exists concerning recurrent stroke risk and smoking though the increased risk of stroke associated with smoking is generally acknowledged. However, it is less well recognized that considerable scientific evidence implicates a strong dose-response relationship between smoking and stroke risk. Shah RS and Cole JW summarize the information regarding smoking-related stroke risk, their dose-response relationship, and the costs for the individual and society [89]. The data concerning hyperglycemic control in DM patients, smoking, and recurrent stroke risk association is currently lacking.

This chapter has summarized the microvascular and macrovascular complications of DM as well as the complex pathophysiologic changes that occur at the cellular level which make diabetic patients at high risk for ischemic stroke. An overview of the epidemiological concerns about DM and stroke was discussed. Also, the remarkable role of hyperglycemia in acute ischemic stroke was revised. Primary prevention of stroke in diabetic centers around the key concept of normoglycemia maintenance which in turn leads to the indirect regulation of concomitant risk factors for ischemic stroke such as hyperlipidemia and hypertension. Optimization of glucose control via oral antihyperglycemic medications is an important facet for hyperglycemia control. Considering the limited number of therapies available for prevention and treatment of stroke and the substantial attendant disability and impact on patients and their families, recent data meaningfully supports the consideration of GLP-1 receptor agonists for stroke prevention in people with type 2 diabetes at increased cardiovascular risk [54]. In patients with established atherosclerotic cardiovascular disease, including ischemic stroke, when prevention of further vascular events is the priority, GLP-1 receptor agonist therapy should be added to metformin independently of

baseline HbA1c. Secondary stroke prevention in diabetes again centers around achieving euglycemia to reduce recurrent stroke risk though there is even less evidence about optimization of risk factors than in primary stroke prevention.

Multiple Choice Questions

1. By comparison to the general population, the risk of mortality from stroke in patients with diabetes is:
   (a) Equal
   (b) Lower
   (c) **Two times higher**
   (d) **Three times higher**
   (e) Four times higher
2. Microvascular changes due to hyperglycemia occur:
   (a) Due to atherosclerosis
   (b) Due to intracapillary thrombosis
   (c) Due to production of reactive oxygen species at the cellular and genetic level
   (d) Due to persistent hyperglycemia
   (e) Due to intracapillary hypertension
3. By comparison of many systemic cells, endothelial cells:
   (a) **Express non-insulin GLUTs which allow for continued generation of ROS**
   (b) Downregulate glucose transporters to prevent continued prevention of ROS
   (c) Are highly resistant to the entrance of glucose
   (d) Express insulin-dependent GLUTs
   (e) Express unique GLUTs
4. Endothelial cell dysfunction results from:
   (a) Deposition of AGEs
   (b) Glycation of LDL
   (c) Increased expression of CD36 in monocytes
   (d) Upregulation of inflammatory proteins
   (e) **All of the above**
5. One of the first studies demonstrating that strict regulation of blood glucose prevented vascular complications was:
   (a) The DCCT trial
   (b) **UKPDS**
   (c) ACCORD
   (d) ADVANCE
   (e) VADT
6. Deleterious endothelial changes develop earlier:
   (a) In carotid arteries
   (b) In basilar arteries
   (c) **In cerebral arterioles**
   (d) In anterior cerebral arteries
   (e) In posterior cerebral arteries
7. Risk factors for ischemic stroke include the following except for:
   (a) **Microalbuminuria**
   (b) Sleep apnea
   (c) Atrial fibrillation
   (d) Hypertension
   (e) Smoking
8. Primary stroke prevention is dependent on:
   (a) An HbA1C target <7.0%
   (b) Monitoring fasting serum glucose
   (c) Monitoring postprandial glucose
   (d) **All of the above**
   (e) None of the above
9. In the UKPDS trial, patients treated with metformin showed:
   (a) A 24% relative risk reduction in ischemic stroke
   (b) **A 32% relative risk reduction in ischemic stroke**
   (c) A 40% reduction in ischemic stroke
   (d) **A 42% reduction in macrovascular deaths related to diabetes**
   (e) A 50% reduction in macrovascular deaths related to diabetes
10. Primary stroke prevention involves:
    (a) *Aggressive blood pressure management should occur in all patients with DM*
    (b) *The use of statins*
    (c) *Smoking cessation*
    (d) Screening and management of atrial fibrillation
    (e) **All of the above**

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Peripheral Arterial Disease and Diabetes Mellitus

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Georges M. Haidar and Boulos Toursarkissian

Epidemiology

While the prevalence of PAD is not as high as that of diabetes, estimated at 5.9% among Americans age 40 and above, its prevalence is elevated to 20–30% among the diabetic population, according to National Health and Nutrition Examination Survey data. In a prospective cohort study of 48,607 men comparing diabetics and nondiabetics and the incidence of developing PAD, the relative risk was found to be 3.39. Even when adjusted for all other risk factors, the RR remained 2.61. Furthermore, the duration of diabetes was directly linked with the risk of developing PAD [1]. Diabetes has also been linked with the development of critical limb-threatening ischemia. The severity of diabetes has also been shown to correlate with PAD risk, with one study in the United Kingdom demonstrating a 28% increased risk of developing PAD with every 1% increase in glycosylated hemoglobin (HgA1c) [2]. Perhaps more importantly, diabetics with diagnosed vascular disease were found to have better management of their cardiovascular risk factors compared to diabetics with occult PAD, highlighting the importance of early recognition [3]. Other risk factors for the development of PAD include smoking, older age, male sex, hypertension, and hyperhomocysteinemia [4].

Diagnostic Challenge

Clinical detection of symptomatic PAD can be made through any number of history and physical exam findings, including claudication, diminished or absent pulses, femoral bruit, cool extremities, distal hair loss, nail thickening, or dependent rubor. Pulse exam in diabetics can be difficult to interpret, and a diminished pulse exam may simply be due to calcification of a vessel without a flow-limiting stenosis. Conversely, a palpable distal pulse does not preclude a more proximal flow-limiting stenosis. Vascular claudication is muscular pain, cramping, fatigue, or heaviness that is induced by walking, is relieved by rest, and is reproducible [5]. Clinical detection of symptomatic PAD in diabetics may be made more difficult by the presence of diabetic sensory neuropathy which may mask claudication symptoms and delay discovery of ischemic tissue loss, and motor neuropathy which may limit mobility enough that claudication is never provoked. Therefore, a careful exam and conscientious use of diagnostic studies are particularly important in the diabetic subset of PAD patients.

PAD is diagnosed and characterized through a variety of modalities inclusive of ankle-brachial index (ABI), duplex ultrasonography, continuous wave Doppler, com-

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Table 52.1 Ankle-brachial index interpretation

ABI	Interpretation
≥1.4	Non-compressible
1.0–1.39	Normal range
0.9–0.99	Borderline
0.7–0.89	Mild disease
0.5–0.69	Moderate disease
<0.5	Severe disease

puted tomography and magnetic resonance angiography, and conventional arteriography. The ABI in particular is well used for its simplicity, noninvasiveness, and reproducibility. ABI is calculated by dividing the larger of bilateral ankle systolic pressures by the larger of bilateral upper arm systolic pressures. Although ranges do not always strictly correlate with the typical interpretations, values help characterize the degree of disease present (Table 52.1).

A report of the National Health and Nutrition Examination Survey found that a value greater than 1.4 is associated with PAD as well [6]. The ABI carries a U-shaped cardiovascular and mortality risk curve, associating higher mortality with values on either side of the normal range.

The diagnostic utility of ABI in diabetics can be more difficult to interpret given that diabetic arteries are not reliably compressible compared to their nondiabetic counterparts due to medial arterial calcification (MAC) particularly in the ankles, resulting in ABI elevation and often normal ABIs in the presence of PAD [7]. In a 2010 study evaluating the validity of ABI in PAD against a multitude of patient characteristics, when compared to lower-extremity angiography, diabetic patients had a 4.36 odds ratio for a normal ABI in the presence of proven PAD [8]. Given the distal and microvascular nature of diabetic angiopathy, there is also a component of microvascular ischemia that is missed when using ABI as the sole diagnostic modality. In a study performed in the United Kingdom, microvascular cutaneous responses were measured in diabetics and nondiabetics with and without PAD, and there was a significant subset of diabetic PAD patients in whom ABIs did not capture the presence of distal microvascular functional abnormalities [9]. This highlights the importance of adjunctive diagnostic modalities in diabetics with suspected PAD despite potentially normal ABI values.

The normal triphasic waveform obtained during noninvasive Doppler testing is characterized by a swift upward wave representing antegrade flow during early systole, a downward wave representing brief retrograde flow during late systole and early diastole, and a small slow upward wave in late diastole. The three phases of the triphasic waveform represent normal antegrade flow and pressure against a compliant vessel wall. The full noninvasive vascular study provides segmental pressures, ABI, and Doppler-derived waveforms (Fig. 52.1).

Alternative modalities have been proposed as adjuncts to the ABI for more accurate and prompt diagnosis of PAD in diabetics. The toe-brachial index (TBI) and toe systolic blood pressure (TSBP) have been investigated on the premise that toe arteries are typically spared of MAC relative to ankle arteries [10]. Brooks et al. found that ABI and TBI were essentially comparable in diagnostic accuracy in diabetics except in the case of overtly calcified crural vessels, proposing that ABI be supplemented with TBI or other adjunct diagnostic modalities when ABI is greater than 1.4 [11]. A major limitation of TBI lies in its less well-defined diagnostic criteria. A review of TBIs in the diagnosis of PAD found that 0.7 is commonly recommended as the lower limit of normal and that the sensitivity of detecting PAD ranged from 90 to 100% and specificity from 65 to 100%. These values however require further large-scale studies to firmly validate these limits [12]. The TBI and TSBP have also been studied as indicators of wound healing potential and amputation risk. A TSBP below 30 mmHg is generally considered insufficient for wound healing, conferring a 3.25-fold risk of nonhealing or amputation [13].

Other noninvasive adjuncts to diagnosis and lesion localization include pulse volume recordings, continuous wave Doppler, duplex ultrasonography, and MR and CT angiography. Continuous wave Doppler, when studied against ABI and TBI, is significantly more sensitive and specific in PAD diagnosis in both diabetics and nondiabetics [14]. This is true especially in infrapopliteal disease [15].

The gold standard of PAD diagnosis had been invasive angiography, although CT angiography is growing more popular due to its less invasive nature as well as its ability to visualize beyond intraluminal defects and provide cross-sectional imaging. Interpretation of CT angiography below the knee can be very challenging in diabetic patients due to the heavy-associated calcification. Conventional angiography provides the benefit of being able to demonstrate lesions and flow dynamics in real time as well as offering the potential for intervention on the spot. However, PAD patients frequently have comorbid cardiovascular disease which puts them at higher risk of adverse outcomes with procedural sedation, not to mention associated diabetic nephropathy which limits the use of intravenous contrast. The risk of the latter can be mitigated through the use of renal protective methods or carbon dioxide angiography; however not all centers have the capability for the latter. Furthermore, CO_2 angiography's ability to demonstrate infrapopliteal lesions, more common to the diabetic population, is inferior to that of iodinated contrast in conventional angiography [16].

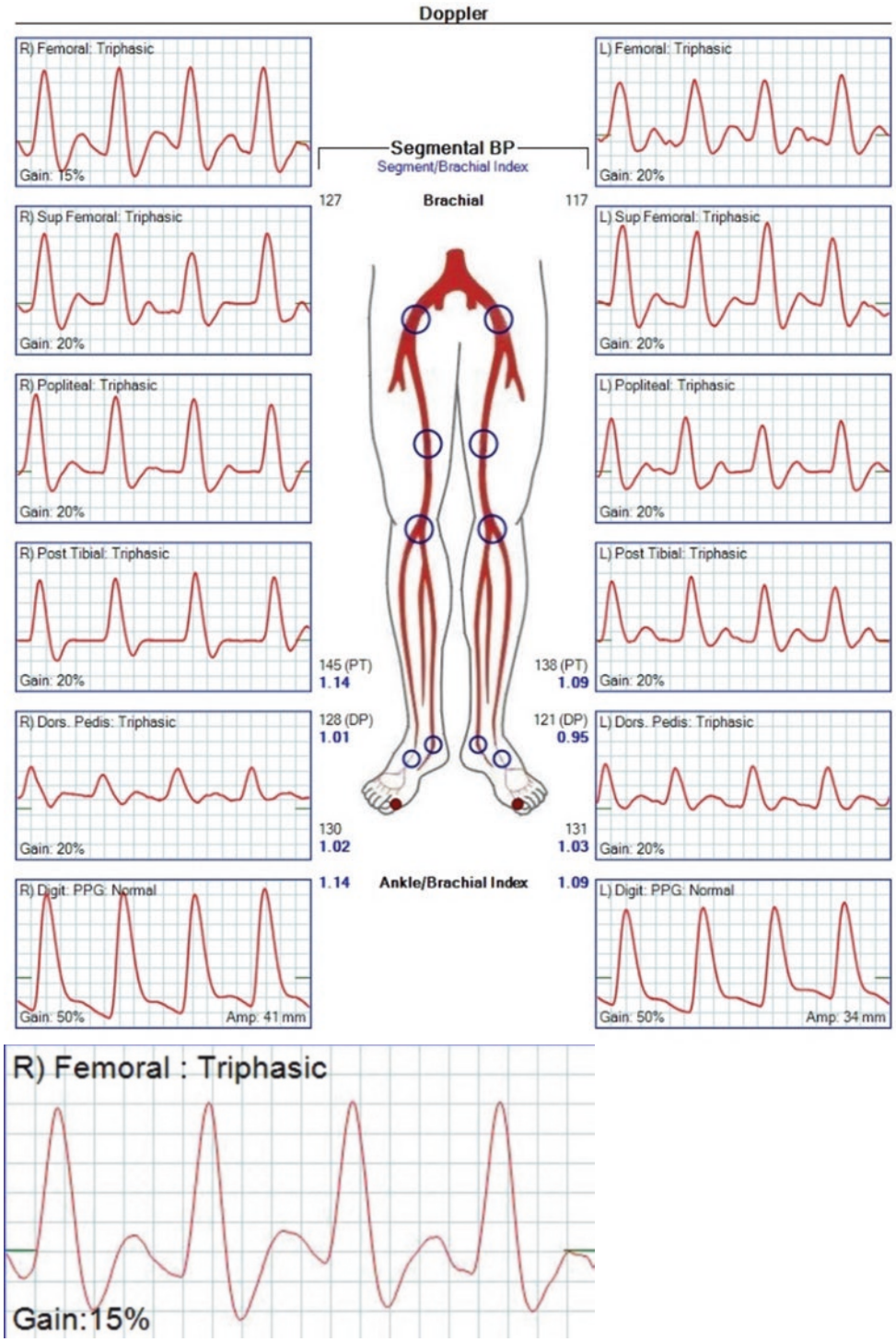

Fig. 52.1 Normal noninvasive study demonstrating Doppler waveforms, segmental pressures, and ABI. Normal triphasic waveforms demonstrate antegrade (1), retrograde (2), and antegrade (3) deflections observed with pulsatile flow through compliant vessels

Pathophysiology, Natural History, and Outcomes

Diabetes is characterized by hyperglycemia secondary to either an autoimmune impairment of insulin production (type I) or a gradually acquired insulin resistance (type II) and results in a number of acute and chronic metabolic derangements that ultimately manifest as microvascular and macrovascular disease that closely intertwines with PAD. As noted, PAD is most commonly due to atherosclerosis, which in turn results from a combination of endothelial dysfunction, vascular inflammation, and medial smooth muscle overgrowth which contributes to the development of flow-limiting lesions [17]. Vascular homeostasis relies

on a functional endothelium which is largely maintained by a steady production of nitric oxide (NO) which functions widely in vasodilatory, anti-inflammatory, antiplatelet, antioxidant, and antiatherogenic capacities. When dysfunctional, the vessel becomes vulnerable to atherosclerosis and thrombosis. Hyperglycemia promotes increased production of reactive oxygen species, which in turn blunts NO bioavailability as well as encourages smooth muscle cell hyperplasia and strongly predicts adverse cardiovascular events [17].

Not only on a cellular level do diabetes and PAD overlap, but they also demonstrate closely related clinical sequelae. Both diabetes and PAD are coronary artery disease risk equivalents and have well-established relationships with cardiovascular disease. Each disease independently as well as in conjunction increases the risk for major cardiovascular and cerebrovascular events as well as major adverse limb events. The Fremantle Diabetes Study of 1294 diabetics found that an ABI less than 0.9 was an independent predictor (HR 2.91) of first-time diabetes-related lower-extremity amputation over the mean 9.1 years of follow-up [18].

The progression of PAD follows a predictable yet not inevitable course. Two of the most commonly used tools for classifying symptomatic PAD are the Rutherford and the Fontaine classifications which aid in determining the selection of best medical therapy alone versus invasive interventions (Table 52.2).

PAD patients with diabetes are much more likely to present with more severe lower-extremity ulcers (Fig. 52.2), and given the common presence of diabetic sensory neuropathy, these ulcers are more difficult to detect and treat at an early stage. In diabetic patients presenting with critical limb-threatening ischemia (CLTI), 50% will develop CLTI in the contralateral limb within the next 5 years [19]. In a prospective cohort study of 1244 male claudicants followed for a period of up to 15 years, diabetes and ABI were the two strongest clinical factors found to be associated with the development of CLI [20]. Both lower-extremity amputation rates and survival have been demonstrated to be significantly higher in diabetic PAD patients compared to nondiabetic PAD patients [21]. Worsened disease severity relates not only to concomitant risk factors and diabetic vasculopathy but also to the more distal nature of PAD in diabetics. Diabetics more frequently demonstrate densely calcified infrapopliteal disease, making both open and endovascular interventions more challenging. In a study published in 2016 comparing a 10-year all-cause mortality in diabetics versus nondiabetics with and without PAD, the relative risk was 2.51 after age and sex matching [22].

A population-based cohort study of 444 German subjects who underwent a first-time lower-extremity major amputation stratified by diabetes diagnosis demonstrated a time-dependent influence of diabetes on mortality. Early in follow-up, nondiabetics actually demonstrated slightly worse survival compared to diabetics; however, after 2–3 years, the survival curves crossed and diabetic mortality surpassed nondiabetic mortality. The investigators proposed that diag-

Table 52.2 Rutherford classifications of peripheral arterial disease

Grade	Classification	Description
Grade 0	Asymptomatic	Asymptomatic disease may be detected incidentally or as part of a routine screening ABI. This stage is slow and insidious in the majority of patients, and many may not progress out of this. As major limb vessels gradually narrow, a variable amount of collateral disease may develop. It is believed that for every patient with symptomatic PAD, there are six with asymptomatic disease [19]. This unearths two management gaps in that asymptomatic PAD patients with diabetes are grossly underdiagnosed and that asymptomatic PAD patients are significantly undertreated for their cardiovascular risk factors [3]
Grade 1	Mild claudication	As the degree of major limb artery narrowing increases, demand may exceed perfusion to the affected extremity and result in various degrees of intermittent claudication. Patients may begin to complain of exercise-induced cramping, fatigue, or heaviness in the buttock, thigh, or calf. Claudication is highly reproducible and is typically relieved with a couple minutes of rest. With the commonly concomitant presence of diabetes, motor neuropathy, obesity, arthritis, and other comorbidities such as heart failure and coronary artery disease, a patient with diabetes and PAD may not achieve activity levels that are adequate to provoke claudication. Claudication may also be masked by sensory neuropathy. For these reasons, patient history must be actively and thoughtfully evoked, physical exam must be critically obtained, and the comorbidities of the patient carefully must be weighed into the diagnostic algorithm
Grade 2	Moderate claudication	
Grade 3	Severe claudication	
Grade 4	Rest pain	With continued narrowing, ischemic symptoms may occur at rest which marks the beginning of critical limb ischemia. Rest pain is classically described at night when the lower extremities are elevated and perfusion is no longer assisted by gravity. Patient will describe pain with leg elevation that is relieved by dangling the extremity over the edge of the bed or by sleeping in a chair. Again, rest pain may be masked by diabetic sensory neuropathy. The end stage of PAD, beginning with mild ischemic tissue loss to ulceration and gangrene, may result with further progression of PAD or after a minor trauma or infection. Again with diabetic peripheral neuropathy, a mild injury may go unnoticed and enter a vicious cycle of poor wound healing due to poor tissue perfusion
Grade 5	Minor tissue loss	
Grade 6	Gangrene	

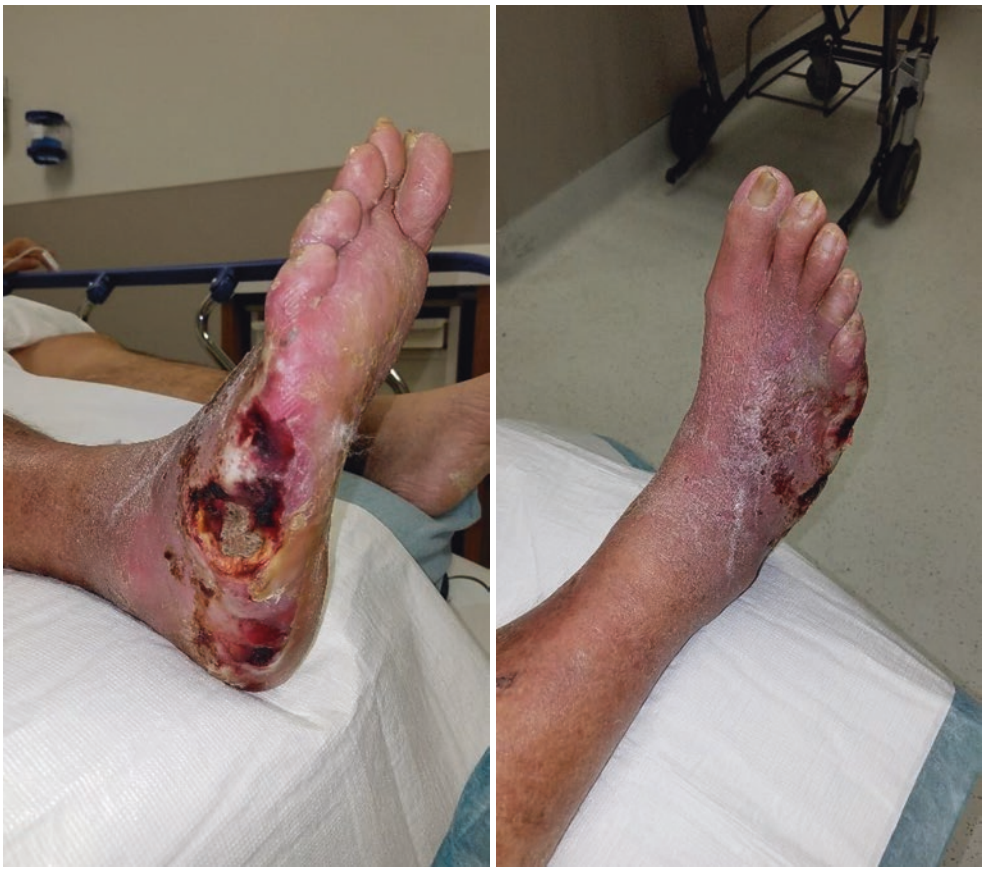

Fig. 52.2 Classic end-stage peripheral arterial disease. Note thickened nails, dependent rubor, and gangrene

nosed diabetics had better general follow-up and were being closely monitored for their diabetes and incidentally any other comorbidities; therefore any issues with wound healing that arose may have been detected and addressed at earlier stages, suggesting that the more malignant natural history of diabetes could be held at bay with aggressive care. They also noted that the diabetic subset had more transtibial amputations, given their infrapopliteal disease, which are associated with better survival outcomes compared to transfemoral amputations [23].

Management

Better characterization of the association between diabetes and PAD strives toward earlier and more accurate diagnosis and subsequent management to achieve two major goals: improvement of lower-extremity symptoms and quality of life (inclusive of avoidance of lower-extremity amputations) as well as minimization of risk for adverse cardiovascular and cerebrovascular events. Management of PAD begins with lifestyle and risk factor modification followed by revascularization treatment algorithms when disease persists despite the former.

Risk Factor Modification

Diabetes

Interestingly, despite diabetes being one of the strongest predictors of PAD development and severity, there is no data to suggest that stringent glycemic control leads to improved outcomes or survival. In a recent meta-analysis, every 1% increase in HbA1c was associated with a 25% increase in CV disease mortality and 15% increase in all-cause mortality. Of the RCTs (randomized controlled trials) reviewed, however, intensive glycemic control never demonstrated improved CV or all-cause mortality [24]. For example, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was a randomized controlled trial that randomized 10,251 subjects to tight (<6.0% HbA1C) and standard (7.0–7.9% HbA1C) glycemic control arms to assess differences in cardiovascular events (nonfatal MI and CVA) and cardiovascular mortality. The tight arm was terminated after only 3.5 years due to an increased mortality rate noted in this arm [25].

Therefore to date, there is no recommendation for tight glucose control in diabetic patients, both with and without cardiovascular disease, and by extension in those with and

without PAD. Current American Diabetes Association guidelines, supported by the American Heart Association, offer a tiered approach to glycemic control, noting 7.0% or lower to be appropriate for most diabetic patients. A goal of 6.5% or lower may be appropriate in younger, healthier patients with less risk factors for hypoglycemia, and conversely a less stringent goal of less than 8.0% is considered appropriate for elder, altered, more frail patients with higher risk for hypoglycemia [26]. No specific recommendations for HbA1c targets in PAD patients exist to this date.

Smoking

The association between smoking and PAD and subsequent progression to CLI, amputation, CV events, and death has been well established, and it has time and again been implicated as the strongest and most preventable risk factor for the development of PAD. The Society for Vascular Surgery practice guidelines for the management of asymptomatic PAD and claudication identify smoking cessation as a GRADE 1A recommendation [27]. Not only is there a 2.2-fold increased risk of symptomatic PAD in active smokers versus nonsmokers, but there is also a significantly increased prevalence of PAD in former smokes compared to never-smokers, thus further emphasizing the importance of prevention in addition to cessation [28].

There is also a clear survival benefit with cessation. An observational cohort study of 739 patients with symptomatic PAD followed quitters versus nonquitters after lower-extremity angiography. Thirty percent were able to quit and maintain cessation 1 year out from angiography, and at a 5-year follow-up, quitters demonstrated significantly lower all-cause mortality (14% versus 31%) and higher amputation-free survival (81% versus 60%) compared to nonquitters [29]. Furthermore, patients who smoke and do require lower-extremity revascularization of any kind are at higher risk of failed intervention and postprocedural complications. A retrospective study of 15,534 patients who underwent infrainguinal bypass found significantly increased 30-day graft failure rates in smokers versus nonsmokers [8].

Despite the mountains of evidence in support of smoking cessation, tobacco use remains widely prevalent in the PAD population. From 2010 to 2015, 101,055 open and endovascular revascularization procedures were cataloged for smoking prevalence and cessation rates after intervention. At the time of intervention, 44% of patients were active smokers. Smoking was more prevalent among males, younger patients, and private insurance carriers. Smokers were also more likely to have lower overall medication compliance. At a 1-year follow-up, 36% of the smokers had quit—of these quitters, they were more likely to be older than 70, have an ABI > 0.9, and have undergone a bypass procedure rather than a percutaneous intervention [30]. Given the demographic findings of PAD patients who are most likely to be active smokers, this gives insight into targeted opportunities for prevention of disease progression through smoking cessation efforts.

Unfortunately, cessation is difficult to achieve and maintain, as demonstrated by multiple studies observing cessation efforts. A key issue identified is the clinician's preconceived belief that long-time smokers are unlikely to quit and that therefore efforts to promote cessation are futile [31]. A cluster-randomized trial of 156 tobacco-using patients at eight vascular surgery practices compared standard counseling to protocolized cessation counseling that included surgeon-driven cessation advice, prescriptions for cessation aids, and referral to a cessation hotline. At a 3-month follow-up, the intervention group demonstrated higher interest in quitting and better knowledge of the negative health effects of smoking [32]. This demonstrated that even with minimal intervention from the surgeon, there was a significant improvement in patient mindset with regard to smoking cessation.

Positive results have been found with intensive cessation regimens targeted at PAD patients. A study in 2 Minnesota vascular centers randomized 124 active smokers with PAD who expressed a desire to quit to intensive and minimal intervention groups. The intensive intervention group included counseling from the vascular provider to quit smoking, multiple sessions with a smoking cessation counselor providing education about smoking and PAD development and progression, offers of cessation pharmacotherapy, and identification of an outside social support person to facilitate cessation efforts. The minimal intervention group received a single admonishment to quit smoking and a list of referrals for outside cessation resources. At a 6-month follow-up, the intensive intervention group had biochemically verified quit rates of 21.3% compared to 6.8% in the minimal intervention group [33].

Hypertension

Numerous large-scale studies have demonstrated an overall decrease in adverse CV events including stroke and MI, chronic kidney disease, and mortality with improved blood pressure control [34]. Hypertension is also an independent risk factor for PAD; however, the association is not as strong as that of smoking and diabetes. The treatment of hypertension is mainly aimed at reducing the risk of adverse cardiovascular and cerebrovascular events and death. That said, the Treatment of Mild Hypertension Study demonstrated that pharmacologic antihypertensive

therapy in addition to dietary changes was associated with a decreased prevalence of intermittent claudication compared to dietary changes alone [35]. This is in contradiction to the theoretical concern that decreased systemic pressure may exacerbate symptomatic PAD due to decreased peripheral perfusion. The benefit of antihypertensive medications is clear; the choice of drug class is slightly murkier in the context of PAD. There existed debate about beta-blockers and their potential for worsening claudication—to date there is no clear evidence to support this, and in fact, a meta-analysis of 11 randomized trials found no association between beta-blockers and adverse effects on walking distance or claudication symptoms [36]. In the appropriate cardiac context, beta-blockers may be the preferred agent for antihypertensive control in PAD patients. That said, angiotensin-converting enzyme inhibitors (ACEIs) also demonstrate clear cardiac and renal protective effects and are potential for the improvement of claudication symptoms. The Heart Outcomes Prevention Evaluation study showed a 25% reduction of cardiac events with ramipril. A double-blind placebo-controlled trial in Australia demonstrated improvements in pain-free walk distance as well as maximum walk distance with ramipril versus placebo; however, this finding has not been reproduced in larger, long-term studies [37].

Dyslipidemia

Dyslipidemia is associated with a higher risk of adverse cardiovascular events, and reduction of cholesterol similarly reduces this risk. The Scandinavian Simvastatin Survival Study (4S) demonstrated that in patients with coronary artery disease, treatment with simvastatin was associated with a relative risk reduction of 42% for CAD-related death and 30% for all-cause mortality [38]. Many studies in the statin era have corroborated this finding and have even found cardiovascular benefits even in those patients with normal cholesterol levels. The pleiotropic effects of statins have been demonstrated in many large-scale, long-term studies.

Treatment of elevated low-density lipoprotein (LDL) has also been strongly implicated in slowing the progression of peripheral atherosclerotic disease burden as well as symptoms of PAD. In the Heart Protection Study, 6748 adults with PAD were randomized double-blindly to 40 mg of simvastatin daily versus placebo and followed for a mean of 5 years. The simvastatin arm demonstrated a 22% relative reduction in the rate of first major vascular event, defined as coronary artery events, strokes, or peripheral vascular events; and it showed a 16% relative reduction specifically for peripheral vascular events. The subgroup with normal LDL levels was conferred protection from adverse vascular events, suggesting as before that statin therapy's benefits extend beyond lowering serum lipid levels [39]. Some of these cholesterol-independent effects involve restoring endothelial function, stabilizing atherosclerotic plaques, and decreasing oxidative stress and vessel inflammation; however, the pleiotropic effects of statin therapy are incompletely understood [40].

The use of statins has also been implicated strongly in the improvement of claudication. A prospective study of 392 patients with PAD compared lower-extremity functional performance between statin users and nonusers. When controlled for age, sex, comorbidities, health insurance, and education, statin users had significantly better lower-extremity functioning compared to statin nonusers. Leg function was measured using 6-min walking distance, 4-m walking speed, time to rise from a chair 5 times in a row, and standing balance [41]. A randomized trial of simvastatin versus placebo in symptomatic PAD patients demonstrated significant increases at 6 months and 12 months (24% and 42%, respectively) in treadmill exercise time until onset of claudication symptoms in the simvastatin arm. No significant differences in treadmill times were noted in the placebo arm at 6 or 12 months [42].

A study of 49 patients comparing 6-min walk test and treadmill exercise time until onset of claudication to real-life self-reported outdoor equivalents and noted no significant difference between the treadmill and outdoor values. Interestingly, based on subjects' responses on the Vascular Quality of Life Questionnaire, the 6-min walk test was the only test modality that correlated with quality of life assessments [43]. Unless patients notice intolerable side effects, statin use is indicated for the reduction in disease progression and mortality as well as for the improvement in quality of life and amputation-free survival in all PAD patients, regardless of serum cholesterol levels. Current recommendations provide goal LDL of less than 100 mg/dL for patients with PAD and less than 70 mg/dL for very high-risk individuals [44].

Obesity

Obesity is most frequently quantified with the body mass index (BMI), which is calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). Being overweight or obese has been associated with increased all-cause mortality [45]. A compilation of 19 prospective study participants totaling 1.46 million subjects found an inverse relationship between BMI and all-cause mortality, with the lowest all-cause mortality rate in the BMI range of 20–24.9 [46]. While obesity has not been directly linked as a risk factor for PAD or adverse lower-extremity outcomes, weight loss in obese PAD patients can

improve claudication symptoms by reducing weight and stress on the lower extremities.

A prospective study of 297 patients with symptomatic PAD characterized factors associated with various degrees of sedentary lifestyles and noted that the most sedentary subjects had higher BMI and diabetes prevalence as well as lower walking economy and maximum walking distance [47]. Another study of 46 symptomatic PAD patients compared subjects with normal weight and those with risk of obesity (BMI 28 or greater). Investigators compared claudication times and total walking times as well as time to recovery of baseline ABI. The risk of obesity subset had shorter times to onset of claudication as well as longer delays in recovery of baseline ABI after exercise [48]. PAD patients should be counseled to maintain healthy body weight to reduce mortality, decrease risk of diabetes, and possibly improve claudication symptoms.

Exercise

In an effort to avoid symptoms of claudication, patients may self-limit their activity level. Numerous studies have shown that sedentary lifestyle is not only linked with overall poorer outcomes, but it is also associated with decreased walking distance and quality of life [49]. A study following activity levels of subjects with PAD demonstrated that higher physical activity level was associated with lower all-cause and cardiovascular disease mortality in the studied population [50]. Simple verbal prescription of a home exercise regimen is insufficient. Patients have various obstacles including poor adherence and fear that the pain of mild claudication is deleterious which require supervision and positive feedback from a clinician vital to the success of any walking program.

Similar to smoking cessation, a simple admonishment to continue walking is not as effective as supervised exercise therapy (SET) [51]. The Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) study is a multicenter randomized prospective trial comparing supervised exercise to endovascular revascularization and best medical therapy. It was found that both SET and stent revascularization improved peak walking times similarly, and both were significantly superior to best medical therapy alone in terms of improved exercise tolerance [52].

The safety of SET has been studied given PAD patients' higher baseline risk of adverse cardiovascular events and mortality. A large-scale review of clinical trials studying SET compiling a collective 82,725 h of training found that a total of 8 adverse events were reported, only 6 of which were cardiovascular in origin [53]. The safety of SET and its exceedingly low complication rate is likely related to its supervised nature.

Antiplatelets

Antiplatelet therapy is recommended to reduce risk of both fatal and nonfatal CV events in patients with symptomatic PAD. The Antiplatelet Trialists' Collaboration, an analysis of combined data from over 135,000 subjects, determined that prolonged antiplatelet therapy with aspirin was associated with a significant 25% reduction in adverse vascular events in high-risk subjects. More to the point, when looking at symptomatic PAD patients specifically, there was an association with significantly reduced overall vascular occlusion rates in the antiplatelet group versus controls (15.7% versus 24.9%), as well as when broken down to native (19.5% versus 39%) and graft (15.8% versus 23.6%) patency rates [54].

While antiplatelet use has been well supported in the literature for secondary prevention in appropriate patients, its use as a primary preventative measure in PAD and diabetes patients has not yet been as well established.

The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial was a blinded, randomized placebo-controlled trial of aspirin and antioxidants (alone and in combination) compared to placebo in diabetics with asymptomatic PAD as defined by abnormal ABI but no symptomatic cardiovascular disease. It demonstrated no difference in primary endpoints (nonfatal MI or CVA, major amputation, death from MI or CVA) in the aspirin and non-aspirin arms, providing no evidence in support of aspirin use for primary prevention of these events in diabetics with subclinical PAD [55]. The ASCEND (A Study of Cardiovascular Events in Diabetes) trial looked at the role of aspirin for cardiovascular prevention in diabetic patients over the age of 40 and without established cardiovascular disease [56]. Aspirin use resulted in an absolute reduction of 0.17% per year in MI, stroke, TIA, and death, at the cost of an excess annual risk of bleeding of 0.13%. A 2016 meta-analysis of six studies evaluating aspirin's safety and efficacy in primary prevention of adverse vascular events was unable to find a difference between aspirin and placebo in these vascular endpoints [57]. As a result, there have been some suggestions that aspirin use be limited to those with added risk factors such as positive family history, high coronary calcium score, elevated lipoprotein A1, or other inflammatory markers [56].

A subset of PAD patients exists that continues to experience adverse vascular events despite long-term aspirin therapy. Symptomatic PAD patients on long-term aspirin were studied prospectively for aspirin responsiveness and adverse vascular outcomes for a period of up to 2 years. Aspirin responsiveness was determined by performing a platelet function test, and 25.8% of study participants were found to be aspirin-resistant. Primary adverse endpoints were more likely in the aspirin-resistant group compared to the aspirin-responsive group (32.3% versus 14.6%). The secondary end-

point of peripheral revascularization or tissue loss was not significantly different between the two groups. This study suggested that aspirin resistance is not only highly prevalent among the symptomatic PAD population but that resistance is an independent predictor of adverse vascular events and mortality, raising the question that these patients may be better served with alternative antiplatelet agents [58].

A number of alternative antiplatelet agents exist today. Clopidogrel is the oldest and most studied of these medications. The Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial was a blinded, randomized trial that compared efficacy of aspirin and clopidogrel in preventing major adverse vascular events and mortality in a population of subjects with symptomatic PAD or recent MI or CVA. A relative risk reduction in these primary endpoints was noted in the clopidogrel arm compared to the aspirin arm at a mean follow-up of 1.9 years. In the subset of patients with symptomatic PAD, the relative risk reduction was 23.8% for clopidogrel compared to aspirin [59]. This suggests that clopidogrel may have better efficacy in symptomatic PAD patients.

The CHARISMA(Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) [60] and CASPAR (Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Arterial Disease) [61] trials both demonstrated the superiority of an aspirin/clopidogrel combination over aspirin alone in preventing cardiac and limb events, with no increase in major bleeding complications in patients with established cardiovascular disease. These were not primary prevention trials and were not limited to diabetic patients.

Another newer agent still is vorapaxar which prevents thrombin from binding to the PAR-1 receptor on platelets. It has been shown to be of benefit in secondary prevention in diabetic patients and decreases acute limb ischemia events as compared to other standard antiplatelets agents, at a cost of an increase in some bleeding complications [62].

Pharmacologic Treatment of Claudication

The principle that peripheral vasodilators should relieve ischemic muscular beds has been addressed with various classes of agents (e.g., calcium channel blockers, alpha-blockers, prostaglandin analogues). Effects of these agents on walking distance and claudication have been largely disappointing. The reason for failure of symptomatic relief may be related to the fact that peripheral vascular beds are already maximally dilated in patients with PAD especially during exertion. Cilostazol, on the other hand, has shown a positive impact on claudication and walking distance. A phosphodiesterase III inhibitor decreases smooth muscle tone and platelet aggregation. It is important to note that while it did significantly reduce symptoms of claudication and increase exercise tolerance, it did not have an effect on mortality [63]. According to the 2016 AHA/ACC guidelines on PAD management, 100 mg twice daily of cilostazol is recommended for relief of claudication and improvement in exercise tolerance. The rheologic agent pentoxifylline is no longer recommended as it has failed to demonstrate any benefit in the treatment of claudication [5].

Revascularization

Indications

While most patients with symptomatic PAD generally are able to stabilize or slow disease progression with risk factor modification, 20–30% will have lifestyle-limiting or limb-threatening progression of their disease requiring invasive management [27]. Revascularization in PAD is indicated in lifestyle-limiting claudication or critical limb-threatening ischemia despite best medical therapy. The decision to perform an intervention should also be weighed against the individual patient's comorbidities, especially age and cardiac and renal functions. In claudicants, for instance, the presence of comorbidities such as arthritis, degenerative disc disease, and cardiac disease may negate any potential benefits of a vascular intervention. It is also important to note that objective measures of vascular disease correlate poorly with severity of disability. The ABI, for example, has not been found to correlate with patients' subjective assessment of quality of life [64]. Therefore, the decision to intervene should not be based solely on objective findings of disease severity but rather on the patient's reported level of disability which can then be supported by these objective findings. Invasive interventions on minimally symptomatic or asymptomatic patients are unlikely to provide significant benefit and may cause harm. According to Trans-Atlantic Inter-Society Consensus statements, a revascularization procedure should "avoid a general anesthesia, pose a lesser systemic stress, and have fewer serious complications" [65].

Furthermore, the presence of an ulcer does not always mandate intervention. Prior to revascularization, a distal wound's healing potential must be assessed based on objective parameters. This information is usually available in the patient's diagnostic workup. For instance, an ankle pressure of 70 mmHg is typically sufficient to heal a foot wound; however, in diabetics 90 mmHg might be preferred. A toe pressure of 40 mmHg in nondiabetics and 60 mmHg in diabetics is ideal [66]. Transcutaneous oxygen pressure measurements (TCOM) are also commonly utilized to determine tissue perfusion and wound healing potential. A TCOM greater than 40 mmHg is generally adequate for wound healing [67]. It is important to note

that TCOM values may also be decreased due to systemic perfusion issues such as heart failure and cardiac valvular disease. Edema and infection may also lead to erroneously low values as well.

In multisegment disease, the most proximal significant lesion should be addressed first, which may relieve symptoms without distal interventions. Treatment of isolated infrapopliteal disease is not recommended for relief of intermittent claudication alone, given the higher risks of complications and recurrence. That said, treatment of infrapopliteal lesions is indicated frequently to heal ulcers. Even though these therapies often do not have long-term patency, they can allow enough perfusion to heal tissue loss or to bridge a complicated patient for optimization before more definitive surgical bypass.

Interventional Challenges

As noted previously, interventions on PAD in diabetes present a particular challenge due to disease severity, presence of other comorbidities including CAD and nephropathy, immune suppression predisposing to wound infections, and more distal heavily calcified disease that is both difficult to traverse percutaneously as well as challenging to find a suitable distal bypass target in open surgery. The presence of diabetes also is a risk factor for restenosis after percutaneous revascularization procedures [68].

Despite these challenges, revascularization in diabetics with CLTI is not only feasible but also associated with lower early amputation rates and higher survival compared to late or no intervention. An analysis of 537 diabetics with CLTI found early amputation rates to be significantly lower in those who underwent revascularization compared to those who did not (1.7% versus 51.9%), and those who did not undergo revascularization had severe CV comorbidities that precluded any type of intervention [69]. Therefore, barring any prohibitive systemic comorbidities, prompt intervention as soon as a patient fails best medical therapy is generally recommended in patients with CLTI regardless of diabetes status, given that limb salvage is significantly worse without intervention [70]. A study of 376 patients with CLI comparing diabetics to nondiabetics found that early revascularization was associated with higher amputation-free survival in both groups compared to those with delayed interventions. The accelerated form of atherosclerosis and intimal hyperplasia at intervention sites in diabetics makes early intervention critical [71].

Endovascular Versus Open

The choice of revascularization procedure is dependent on multiple factors including available resources, operator experience, and patient-specific characteristics such as location and severity of the lesions, presence of skin lesions, activity level, comorbidities, compliance, availability of adequate autogenous conduit, and personal preference. Treatment guidelines from the American Heart Association and the revised Trans-Atlantic Inter-Society Consensus document recommend endovascular therapy as the first-line treatment of focal and moderate-length lesions (Fig. 52.3), while bypass is reserved for diffuse or long-segment disease (Fig. 52.4) [72].

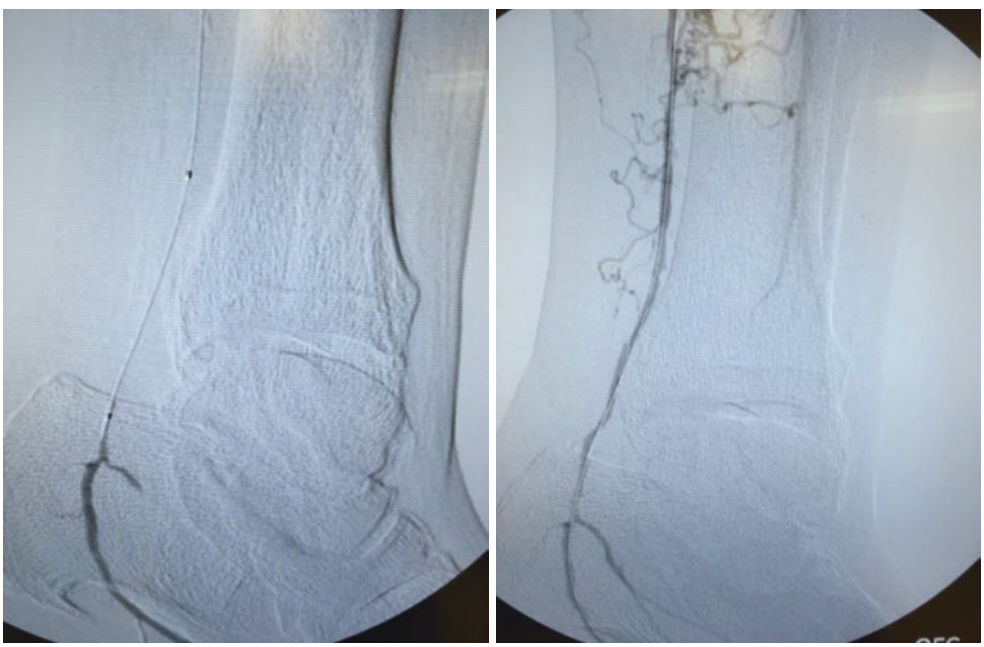

Fig. 52.3 Digital subtraction angiography (DSA) of crural occlusive disease (left) with restoration of inline flow to the foot after angioplasty of the posterior tibial artery (right)

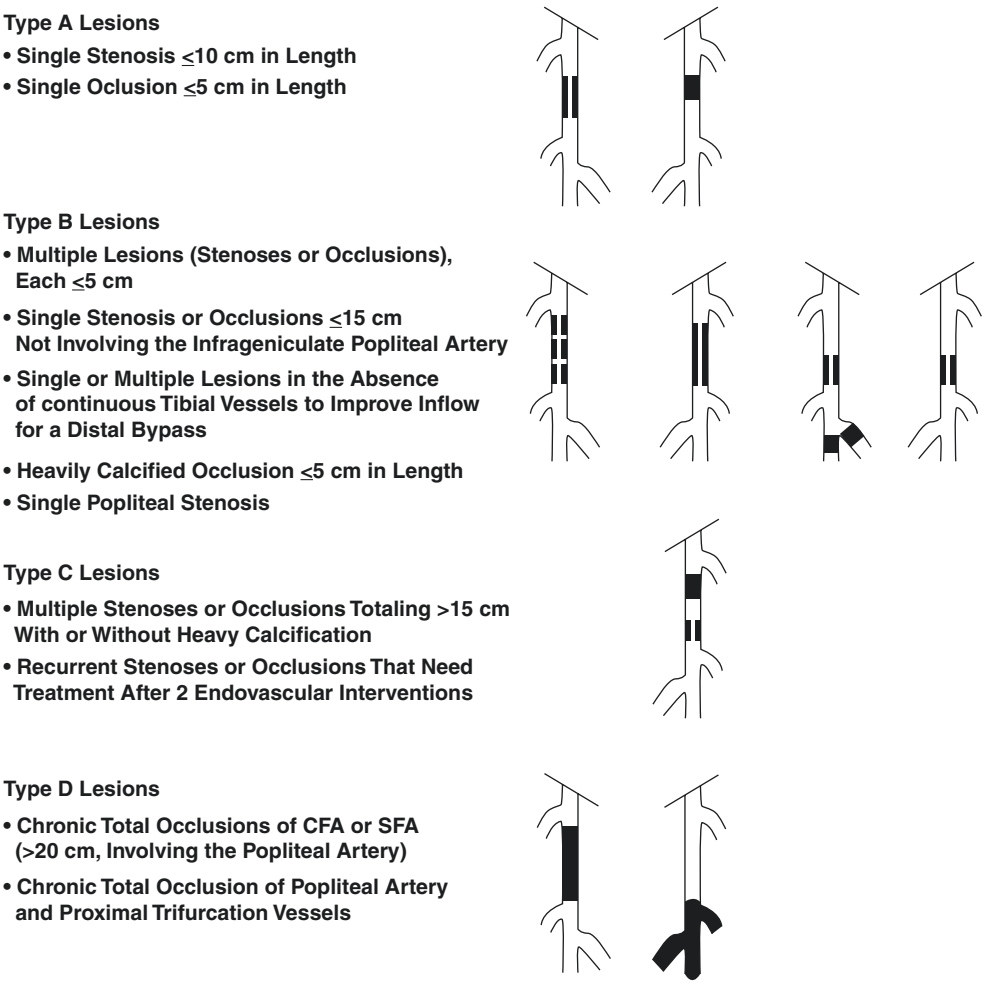

Fig. 52.4 Trans-atlantic Inter-society consensus classifications of femoropopliteal disease

Endovascular and open surgical options should be viewed as complimentary and not necessarily competitive. For example, a patient with severe coronary artery disease with a depressed ejection fraction and poorly controlled diabetes presenting with an ischemic foot ulcer secondary to multi-segment crural disease may not have the physiologic reserve to tolerate open bypass surgery, but tibial angioplasty may provide improved flow and a chance for the ulcer to heal and avoid limb loss or sepsis while the patient undergoes coronary artery bypass and gains better glycemic control.

More recently, with the development of more advanced endovascular techniques in appropriately selected patients, the choice of revascularization modality has had no significant effect on amputation-free survival or all-cause mortality [73]. A systematic review of 57 articles encompassing 9029 patients with diabetic foot ulcers and PAD who had undergone revascularization examined outcomes and characteristics of these patients. Ulcer healing rate was 60% at a 12-month follow-up with any kind of revascularization. In three studies that utilized a PTA-first strategy, mortality and limb salvage rates were comparable to other studies that did not follow a PTA-first strategy, and there was a reported 11% failure rate of endovascular therapy requiring subsequent open bypass [70]. In one study of 1188 diabetics admitted for CLTI, PTA was performed as a first-line intervention in 993 consecutive patients. During a mean follow-up period of 26.2 months, primary patency at 5 years was 88%. The 30-day major amputation rate was 1.7%, and a 5-year survival was 74%, demonstrating in this series a comparable result to open interventions [73]. There are however many other studies that suggest that restenosis rates in diabetics undergoing endovascular interventions are high and that while adequate limb salvage can be achieved, it comes often at the cost of repeated endovascular interventions.

Similar results were demonstrated in a British study. The Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial found that amputation-free survival and all-cause mortality were similar between PAD patients randomized to endovascular and open surgical arms; however, the surgical arm had greater morbidity in the first year. Interestingly, after 2 years, the surgical arm did surpass the endovascular arm in terms of amputation-free sur-

vival. This study reinforced that while endovascular and surgical interventions had equivalent short-term results in terms of revascularization and limb salvage, open bypass provided a more durable yet more morbid treatment option [74]. The BASIL trail was not limited to diabetic patients however.

A single-center series also from the United Kingdom found that with an aggressive multidisciplinary approach to the diabetic patient with CLTI, they were able to yield similar limb salvage and overall survival rates as in the nondiabetic patients [75]. In a retrospective study of 1977 infrainguinal open bypass patients for CLTI, inhospital mortality rates were found to be equivalent between diabetics and nondiabetics. However, rates of major adverse events (major amputations, renal insufficiency, MI, dysrhythmia, CHF, and wound infection) were significantly higher in diabetics [76]. The increased perioperative morbidity of bypass surgery must therefore be weighed against its superior long-term durability during the mindful patient selection process.

There are as of this writing two ongoing trials that specifically compare open and endovascular interventions below the knee (an area where diabetic PAD is common). These are the BASIL-2 trial and the BEST-CLI trial. Hopefully, they will help better select therapies for individual patients.

Percutaneous Therapy

Endovascular interventions continue to push the envelope. Initially only indicated for select, focal, short-segment disease, they are now often used for long-segment total occlusions (Fig. 52.5) and multifocal disease. For example, a patient with severe coronary artery disease with a depressed ejection fraction and poorly controlled diabetes presenting with an ischemic foot ulcer secondary to multi-segment crural disease may not have the physiologic reserve to tolerate open bypass surgery, but tibial angioplasty may provide improved flow and a chance for the ulcer to heal and avoid limb loss or sepsis while the patient undergoes coronary artery bypass and gains better glycemic control.

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Endovascular therapy options include percutaneous balloon angioplasty with or without stent placement, atherectomy, and any combination thereof. There has been some suggestion in registry data that atherectomy may be of benefit in diabetic patients in terms of a reduced restenosis rate. In general, endovascular procedures are well tolerated and result in shorter hospital stays, more rapid recovery, and less wound complications with equivalent limb salvage rates compared to open surgical revascularization in most cases. That said, as noted, endovascular interventions are generally less durable than surgical bypass and more frequently require reintervention to maintain patency [77]. A study observing 101 diabetics with CLTI who underwent endovascular infrapopliteal intervention noted successful PTA in 87.8%. The seven patients in whom PTA failed had heavily calcified, chronically totally occluded lesions that were not amenable to PTA nor to surgical bypass. The 1-year target vessel restenosis rate was 42%. However, over a mean follow-up of 2.9 years, major amputations occurred in only 7%, and all-cause mortality was 5% [78]. The major amputation rate in this series is comparable to that in another series of 508 diabetics with CLTI who underwent revascularization, with no distinction between endovascular and open, in which 10.3% underwent major lower-extremity amputation [19]. These series demonstrate the utility of endovascular interventions in terms of limb salvage despite high rates of target vessel reocclusion. Diabetes has been shown to be a risk factor for lower long-term patency rates following endovascular revascularization [79].

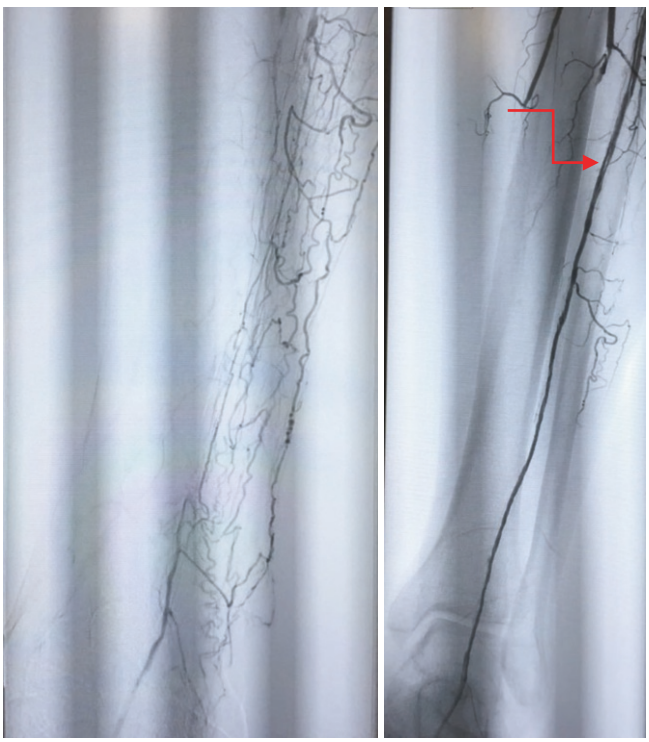

Fig. 52.5 Spidery collateralizations due to infrapopliteal occlusive disease (left). Note their disappearance after angioplasty (right) of the anterior tibial artery (arrow)

The technique of subintimal angioplasty wherein the intima is intentionally dissected and the lesion angioplastied subintimally has been used with some success in chronic total occlusions which either precluded or failed PTA or open bypass attempts. Technical success rates typically range between 80 and 90%, with notably worse outcomes in CLTI compared to claudication, and primary patency rates at 1 year range from 56 to 70% [80]. Ulcer healing rates have been excellent as well, cited at 75% over a mean 23-month follow-up for a series of 60 consecutive diabetic patients with CLTI who were deemed unfit for surgical bypass. This is comparable to ulcer healing rates with open bypass surgery [81]. A recent study in China examined the outcomes for subintimal angioplasty in diabetics with chronic distal (dorsalis pedis or plantar artery) occlusive CLI who were deemed poor candidates for open bypass or PTA. Thirty-seven such patients underwent subintimal angioplasty with an 83% success rate and 95% 1-year limb salvage rate. Complications occurred in 13% of these patients, the most common being vessel perforation followed by failed reentry [82].

Stents are sometimes needed when an angioplasty fails because of recoil or flow-limiting dissection. Critical to stent patency is the maintenance of lifestyle modifications and antiplatelet therapy. The MIRROR (Minimally Invasive IntRaceRebral HemORrhage) study, a randomized, double-blinded study of 80 patients who underwent percutaneous intervention (with and without stent placement), studied dual antiplatelet therapy (DAT) with aspirin and clopidogrel versus aspirin alone. Primary endpoints were direct measurements of two platelet activation factors from whole blood samples taken from subjects after loading doses and just before intervention as well as clinical outcome at 6 months. Markers of platelet activity were lower in the DAT group and recurrence of disease in the target lesion was lower [83]. The findings of this study favor DAT over aspirin monotherapy in PAD after endovascular stent therapy.

More recent developments in angioplasty have included the use of drug-coated angioplasty balloons to prevent restenosis. The main drug used is paclitaxel which prevents smooth muscle proliferation that causes intimal hyperplasia and recurrent stenosis. Drug-coated angioplasty has shown benefits in improving primary patency when used in the superficial femoral artery, but the results have not been as encouraging to date in the vessels below the knee (where diabetics have a high rate of atherosclerotic burden) [84].

A review of 14 randomized trials of antiplatelet therapies around the time of peripheral vascular interventions concluded that aspirin should be administered 6–24 h before PTA and continued afterward to reduce periprocedural thromboembolic events. Regarding DAT versus aspirin alone, a commonly adopted practice was noted to be indefinite use of aspirin as well as 4 weeks of post-procedural clopidogrel given the benefit noted in multiple studies with loading doses of aspirin and clopidogrel [85]. However, more long-term studies comparing dual versus monotherapy as well as long-term outcomes with newer antiplatelet agents are needed prior to making recommendation changes regarding antiplatelet therapy in PAD.

Open Surgery

Bypass surgery is the gold standard intervention for symptomatic PAD, and while it is being supplanted by the rapidly growing use of endovascular therapies, its efficacy in restoring inflow and relieving claudication symptoms and salvaging limbs is undisputed. In fact, despite the growing popularity of utilizing endovascular-first treatment algorithms, a recent retrospective analysis found that in comparing propensity-matched lower-extremity bypass versus endovascular intervention for CLTI, the former was associated with a significantly lower rate of 30-day major adverse limb events and no higher rate of 30-day major adverse cardiovascular events [85]. Therefore, it cannot be dismissed as an unjustifiably risky invasive intervention in appropriately selected patients. Lower-extremity bypass also remains the solution for lesions that are not traversable percutaneously or have failed previous percutaneous interventions. Its use is limited by severe systemic illness (e.g., severe heart failure) that may pose unacceptable operative risk, lack of adequate bypass conduit, and presence of active infection or sepsis (a commonality in diabetic CLTI patients). It is estimated that about 30% of CLTI patients will need a surgical bypass.

The best outcomes for open bypass surgery are obtained using a one-piece greater saphenous vein as the conduit. Conduit choices are as follows in order of preference: ipsilateral greater saphenous vein, contralateral greater saphenous vein, composite (spliced) vein grafts, lesser saphenous vein or arm vein, and nonautologous vein or synthetic graft. Up to 40% of bypass candidates lack adequate ipsilateral greater saphenous vein conduit and require an alternative conduit choice.

Again there exists a correlation between diabetes and treatment complications. In a cohort study of 6112 individuals who underwent open lower-extremity bypass, stratified by indication for intervention, insulin-dependent diabetes was associated with a significant 1.27 odds ratio of readmission, the majority (62.9%) of these admissions being for wound complications. This is unsurprising given diabetics' propensity for wound infection [86]. This further emphasizes the importance of perioperative glycemic control in diabetic PAD patients.

Interestingly, diabetes has not been shown to be an independent predictor of decreased bypass graft patency [87]. This finding has been demonstrated in multiple studies,

including the Veterans Affairs National Surgical Quality Improvement Program (VA NSQIP) which identified 14,788 patients who underwent infrainguinal arterial bypass procedures and found that diabetes was in fact significantly protective from early graft failure [88]. The PREVENT III trial, a double-blinded randomized controlled trial of 1404 patients comparing ex vivo application of edifoligide to vein grafts versus placebo just prior to lower-extremity bypass for the prevention of graft failure, found that diabetics, while significantly more likely to present with tissue loss, did not have a higher risk of graft failure at any stage through the 12-month follow-up period [89]. Although diabetes in PAD is independently associated with a higher risk of amputation and mortality, it is not a risk factor for graft failure.

A successful graft depends on adequate inflow, outflow, and conduit quality. Bypass graft failure is classically described in three phases: early (0–30 days), intermediate (30 days to 2 years), and late (beyond 2 years). Early failure is typically attributed to technical factors or judgment error, such as poor conduit, retained venous valves, technical error, and inadequate inflow/outflow. Intermediate failure is secondary to intimal hyperplasia. Some degree of intimal hyperplasia occurs in all grafts; however, where and why this becomes pathologic and flow limiting is not well understood. There is a propensity for this to occur in areas of endothelial trauma (e.g., where a valvulotome was utilized), which strongly suggests that this process is related to a dysfunctional endothelium. Late failure is seen as a progression of the primary atherosclerotic process causing graft narrowing as well as deficiency of inflow and/or outflow.

The incidence of early graft failure is around 5%. This incidence of intermediate failure is 1–2% per month for the first year, and then it further declines to 2–4% per year thereafter. Early surveillance with duplex ultrasonography can detect stenosis before progression to occlusion. A prospective study of 68 lower-extremity vein bypasses in diabetics undergoing intensive postoperative surveillance with duplex ultrasonography found that, after a mean follow-up of 12 months, duplex US (ultrasound) could predict graft thrombosis and amputation [90].

Current literature suggests that some variation of a duplex scan should be done every 3–6 months for the first 1–2 years after bypass, with a follow-up arteriography for abnormal findings. Duplex scan is also indicated specifically if a patient has return of claudication symptoms, ABI decreases by 0.15 from highest postoperative value, or a previously palpable pulse diminishes or disappears. A peak systolic velocity (PSV) greater than 180 cm/s or velocity ratio (V_r) greater than 2 suggests a focal stenosis greater than 50%, while a mean graft velocity less than 45 cm/s indicates a low flow state that is conducive to graft thrombosis. According to Tinder et al., a PSV greater than 300 cm/s or a V_r greater than 3.5 indicates a need for graft revision, and with appropriately tailored surveillance according to an individual graft's risk profile and postoperative duplex scan, this early detection leads to reintervention that prolongs graft patency [91]. While the most recent TASC II guidelines do not recommend routine duplex ultrasonography for lower-extremity bypass (instead they support clinical surveillance through palpation and ABI measurements every 6 months for at least the first 2 years after bypass), multiple studies have demonstrated that surveillance with duplex ultrasonography detects early lesions before progression to thrombosis [92, 93]. Tinder et al. found that more aggressive duplex surveillance for those bypasses with high-risk characteristics or an abnormal first postoperative scan was associated with higher primary-assisted patency and lower graft failure rates [94].

Patency, while important as a metric of durability, is not the only measure of a revascularization's success. Likewise limb salvage and mortality, while the typical primary outcomes, are not the only measures of patient satisfaction and quality of life. The PREVENT III trial established quality of life as a secondary endpoint and noted that after lower-extremity bypass, quality of life as assessed by the Vascular Quality of Life Questionnaire improved progressively at 0, 3, and 12 months postoperatively [89]. Another study comparing objective measures of lower-extremity function and patient perceptions of quality of life found that while objective measures such as knee flexion and extension, a 6-min walk distance, walking speed, and balance showed absolute improvements, none reached statistical significance. Despite this, there was a significant improvement of subjective quality of life and pain perception postoperatively [95].

Areas of Current Interest

Figure 52.6 summarizes a current algorithm for approaching diabetic patients with suspected peripheral arterial disease. One of the major limitations in interpreting all the studies in PAD and DM has been the inherent difficulty in having truly equivalent groups in whom to compare open and endovascular interventions. In addition to PAD, the major factors that increase the risk of limb loss are the presence of foot infection and the existence of a foot wound and its extent. In an effort to account for this, a WIFi score has been proposed, which included an assessment of the Wound, any Ischemia, and Foot infection [96]. Each category is scored from 0 to 3, and a final score is obtained allowing classification of each limb into one of four categories. Limbs staged as I are considered as low risk for limb loss while those classified as IV are considered high risk for limb loss, with known predicted limb loss rates. Each limb can be restaged following revascularization or control of infection, thereby producing a new estimated risk of limb loss. The system allows for meaningful benchmarking of results and counselling of patients.

Diabetes and PAD are not only frequently comorbid but also result in an accelerated natural history and more com-

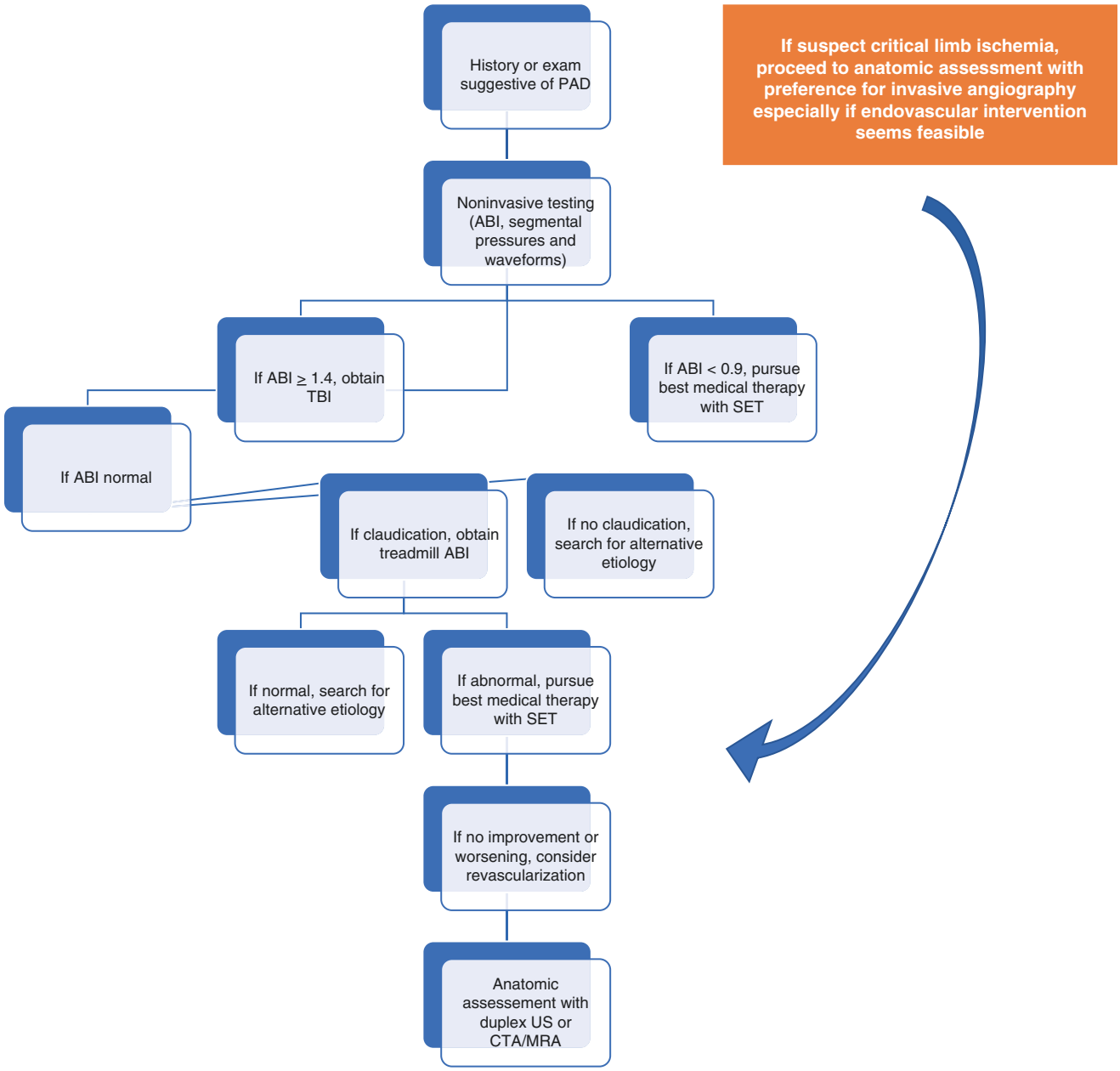

Fig. 52.6 Algorithm for suspected PAD

plicated outcomes and mortality after intervention. Therefore treatment of these patients begins with an appreciation of the significance and risk involved with their comorbidity and the importance of early intervention with lifestyle and risk factor modification. That said, once lower-extremity disease has progressed to the point of requiring an invasive intervention, the presence of diabetes should not deter attempts at revascularization. Treatment options have and continue to become more sophisticated, and with an aggressive multidisciplinary approach, they have the potential to yield noninferior outcomes in the diabetic population.

Multiple Choice Questions

1. Which of the following is *not* a known risk factor for atherosclerotic peripheral arterial disease?
   (a) Smoking
   (b) Age
   (c) Diabetes
   (d) **Trauma**
   (e) Hyperhomocysteinemia
2. According to NHANES (National Health and Nutrition Examination Survey) data, what is the prevalence of peripheral arterial disease in the general population?

(a) 1%
(b) **6%**
(c) 29%
(d) 50%
(e) 85%

3. Which of the following constitutes an abnormal ankle-brachial index?
   (a) 1.0
   (b) 0.6
   (c) 1.5
   (d) A and B
   (e) **B and C**
4. History and physical exam findings of peripheral arterial disease include all of the following *except*:
   (a) Lower-extremity claudication
   (b) Diminished pulse exam
   (c) Hair loss
   (d) Dependent rubor
   (e) **Pain with lower-extremity elevation**
5. Diabetics with peripheral arterial disease
   (a) Should aim for a hemoglobin A1c level of 5%
   (b) **Are at higher risk for limb loss than nondiabetics with peripheral arterial disease**
   (c) Should have regular CT angiograms to monitor their disease burden
   (d) Have reliable pulse exams for detecting the presence of flow-limiting lesions
   (e) Do not benefit from supervised exercise therapy programs because of the risk of falling
6. Critical limb ischemia
   (a) Is defined by the presence of rest pain and/or tissue loss secondary to a flow-limiting lesion
   (b) Represents the end stage of peripheral arterial disease
   (c) Risk increases with comorbid diabetes
   (d) Can be masked by diabetic neuropathy
   (e) **All of the above**
7. Constitutive production of nitric oxide by a functional endothelium confers upon the vessel antiplatelet, anti-atherogenic, vasodilatory, and anti-inflammatory properties.
   (a) **True**
   (b) False
8. Pharmacotherapy for intermittent claudication has been shown to be effective in reversing atherosclerotic disease progression.
   (a) True
   (b) **False**
9. Percutaneous intervention for lower-extremity peripheral arterial disease is:
   (a) Reserved only for frail patients unfit for the morbidity of open surgical bypass
   (b) Absolutely contraindicated in cases of completely occlusive lesions
   (c) **Less durable than open bypass in the long term**
   (d) Not recommended in diabetic patients due to inferior outcomes
   (e) Associated with higher amputation rates compared to open surgical bypass
10. Open surgical bypass
    (a) Is reserved only for severe critical limb ischemia
    (b) **Requires adequate inflow and outflow as well as an appropriate conduit**
    (c) Can achieve equivalent results using autogenous vein and synthetic grafts
    (d) Is a definitive treatment and does not require regular surveillance

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Ophthalmic Disease in Diabetes

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Abbreviations

Anti-VEGF IV	Anti-VEGF intravitreous injection
BCVA	Best corrected visual acuity
BMI	Body mass index
CRT	Central retinal thickness
DM	Diabetes mellitus
DME	Diabetic macular edema
DR	Diabetic retinopathy
DRS	Diabetic retinopathy study
ESASO	European School for Advanced Studies in Ophthalmology
ESR	Erythrocyte sedimentation rate
ETDRS	Early Treatment Diabetic Retinopathy Study
GADA	Glutamic acid decarboxylase antibodies
HOMA-B	Homoeostasis model assessment estimates of β-cell function
HOMA-IS	Homeostasis model assessment estimate of insulin sensitivity
MA	Microaneurysm
NPDR	Nonproliferative diabetic retinopathy
OCTA	Optical coherence tomography angiography
PDR	Proliferative diabetic retinopathy
PEDF	Pigment epithelium-derived factor
PEVAC	Perifoveal exudative vascular anomalous complex
CRP	C-reactive protein
RDR	Referable diabetic retinopathy
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VTDR	Vision-threatening diabetic retinopathy

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Introduction

Diabetes mellitus (DM) is a chronic multisystemic metabolic disease, which is an effect of persistent hyperglycemia and causes deleterious effects in the micro- and macrovasculature [1–4]. It is expected that its incidence and prevalence will continue to increase globally, making it one of the great pandemics of the twenty-first century [5–8].

The eye is one of the main organs affected by this pathology, mainly causing diabetic retinopathy (DR), which is one of the most important microvascular complications of DM [2, 3, 9]. DR has been reported to be one of the leading causes of blindness in the working age population [10–15]. From 1990 to 2010, in England, as a result of the policies of screening and early treatment, DR is no longer considered as the leading cause of blindness and moderate to severe vision loss [16]. Although less known for non-ophthalmologists, there is a spectrum of eye disease related to diabetes that can lead to eye problems or even loss of vision [17–20].

Epidemiology of Diabetes and Diabetic Retinopathy

The diabetic patients are at 25 times more risk of blindness compared to nondiabetic individuals. This was documented by a study that estimated untreated proliferative diabetic retinopathy (PDR) results in an irreversible visual loss in 50% of individuals at five years after diagnosis [21]. The impact of this visual dysfunction is globally recognized [13, 18, 21, 22], involving several countries like the UK that has set up screening programs for early detection and treatment of DR [21]. In the literature, although there is some heterogeneity in the epidemiological data on DR [15, 18], there is an agreement on the fact that this is a current problem with a strong public health impact.

A meta-analysis involving 35 studies carried out worldwide from 1980 to 2008 provided data from 22,896 individuals with diabetes. The estimated global prevalence of DR was 34.6%: 6.96% for PDR, 6.81% for diabetic macular edema (DME), and 10.2% for vision-threatening DR (VTDR) [15].

Studies in the European population showed a prevalence of DR of 36.5–93.6% in type 1 diabetes, 16.3–34.2% in type 2, and 16.3–48.8% in mixed cohorts [13], with VTDR prevalence estimated between 6.7 and 34.9% [13].

In population-based studies, the prevalence of DME among patients with type 1 diabetes was between 4.2 and 7.9%. In patients with type 2 diabetes, it was between 1.4 and 12.8% [13]. Non-stereoscopic fundus photography was used in most of the studies, which affected the accuracy of DME assessment. About half of the studies defined macular edema using the clinically significant macular edema (CSME) criteria, and hence, only the more severe spectrum of DME was captured in these studies [13]. A Cochrane review of the prevalence of DME as assessed by optical coherence tomography (OCT) has found a large range of prevalence rates (19–65%) [13]. This should be considered as a new reference standard for assessment of DME, even in some screening settings [23].

Ling et al. [22] indicated a DR prevalence of 49% in type 1 diabetes and 24.2% in type 2 diabetes in the UK, with a global prevalence of 21.4% for NPDR (nonproliferative diabetic retinopathy), 2.8% for PDR (proliferative diabetic retinopathy), and 6.1% for CSME (clinically significant macular edema).

An important topic in epidemiological DR-related studies is the prevalence of VTDR—either PDR and/or DME. According to a meta-analysis study by Yau et al. (2012), VTDR prevalence was found to be 10.2% globally. These patients need referral and urgent treatment. Some of the studies do a segmentation of the two forms of VTDR [13].

Variability in the Results of Epidemiological Studies

The analysis of the results of multiple studies based on a review of Lee et al. [13] revealed that the prevalence varies depending on the geography and studies reflecting the precociousness DR or its late identification with more advanced disease. Also, there is a difference between diabetes type 1 and type 2. Depending on the epidemiological studies carried out on patients, those who visited hospitals showed a higher prevalence of VTDR compared to those from the community (population-based) who showed lower prevalence of DME and PDR. A wide range of prevalence observed may also be due to the differences in healthcare systems and socioeconomic factors between the studied populations. However, conclusions cannot be drawn as key characteristics, such as known duration of diabetes, vary significantly between the sampled populations [13]. The studies performed in newly diagnosed patients have a lower prevalence of DR since it increases with the duration of the diabetes [13, 24]. It is also higher in Western countries due to urbanization, diet, obesity, and sedentarism [13]. Eastern populations (except in the surrounding regions of Singapore) and the less urbanized and industrialized rural areas have a lower prevalence [13].

Incidence and Progression of DR

In the Wisconsin study, Klein et al. [25] evaluated the progression of DR in individuals with type 1 diabetes over a period of 25 years. The authors have documented a cumulative progression rate of DR of 83%, a progression to PDR of

42%, and improvement of DR in 18%. In addition, the cumulative incidence of macular edema and clinically significant macular edema was 29% and 17%, respectively.

In Portugal, Dutra Medeiros et al. [26] proceeded to assess the incidence and progression of DR in a prospective population-based cohort of type 2 diabetics with five years of follow-up. Referral diabetic retinopathy (RDR) was set to all patients classified with moderate to severe NPDR or PDR, with or without maculopathy or mild NPDR with maculopathy (a little more comprehensive than set to VTDR). The annual incidence of any DR in patients without retinopathy at baseline was 4.60% in the first year, reducing to 3.87% in the fifth year; the cumulative incidence at five years was 14.47%. The risk of any degree of DR, non-referable DR, or RDR was strongly associated with increased duration of diabetes and earlier age at diagnosis.

The Impact of the Nordic (European) Diabetic Classification on Screening of Diabetic Retinopathy

Data-driven algorithms reflect a larger heterogeneity in DM subtypes when compared with the classical division into T1DM and T2DM or glycemic and HbA1c level [27]. Recently, Ahlqvist, E. et al. published a study [28] where six variables were used to carry out a CLUSTER ANALYSIS: age at diagnosis, BMI, HbA1c, GADA, C-peptide, and HOMA-B and HOMA-IS. A Cox and logistic regression was made, and they found 5 clusters [28] (Table 53.1).

The groups 4 and 5 corresponded to 62% of the diabetic patients, who have low complications level; this is the reason why it is advisable to screen these patients only every 2 or 3 years. On the other hand, more attention should be paid to the higher-risk group of eye complications, namely, group 2 and group 1 which correspond to the conventional DM1.

Currently, it is not possible to identify these groups, in our daily practice. However, this screening strategy should be implemented as soon as we can routinely use those tests in diabetic patient care.

OCT as a Current Screening Tool and AI as an Adjunct to Screen Activity

In addition, we should incorporate the new trends toward the use of portable or home OCT and current use of AI in the screening of diabetic retinopathy. Indeed, RetMarkerDR software, a CE-marked Class IIa medical device developed in Portugal, has been used in local DR screening for some years [29]. It has been implemented into a co-existing, human grader-based DR screening program conducted in Portugal. In this case, Retmarker is used to select between "disease" and "no disease" groups. A human grader assessment is only needed for the "disease" subgroup, avoiding the use of this time-consuming practice to analyze normal images. The human resources are directed to those who really need surveillance from an ophthalmologist.

Table 53.1 The Nordic study (European study of Ahlqvist, E. et al. (2018) points to a new diabetic classification: five clusters of recently diagnosed diabetic patients were obtained

Cluster	Name	INITIALS	Prevalence %	Characteristics
1	**Severe autoimmune diabetes**	SAID		**High incidence of retinopathy**
2	**Severe insulin-deficient diabetes**	SIDD		**highest incidence of retinopathy**
3	Severe-insulin resistant diabetes	SIRD		
4	Mild obesity-related diabetes	MOD	**22%**	Low complictions level if it do.
5	Mild age-related diabetes	MARD	**40%**	Low complictions level if it do.

The four and five clusters have a low incidence of diabetic complications, namely, eye complications, and correspond at 62% of the diabetic patients. Consequently, the resources should be directed toward the 38% of the patients of the higher risk of developing diabetic retinopathy

OCTA and OCTA as Part of Multimodal Imaging in Diabetic Retinopathy

Structural OCT is a precious tool on assessing DR, showing qualitative and quantitative imaging of macular area and foveal morpho-structure. A multimodal imaging report integrates also IR and color fundus photography, color ultrawide field photography, AF (autofluorescence), en face structural OCT, and OCTA, which can depict the superficial and deep capillary plexus as well as the choroidal plexus. Currently, this multimodal imaging is essential to establish diagnosis and classifying the DR [30].

Diabetic Retinopathy Physiopathology

Several pathophysiological mechanisms are concerned. It is thought that in the retina, there is a change in response to insulin that exists in the peripheral tissues. As a consequence, there is a decrease in the "signaling" PEDG-derived platelet growth factor, which causes a decrease in the survival of pericytes. The capillary walls disappear [31], which has been marked as an early event in the physiopathology of DR. Microstructural and functional changes appear at the vascular and neuronal levels because of the chronic inflammatory state of the retina induced by maintained hyperglycemia. Indeed, it is in the context of the neurovascular retinal unit [32] that the chronic hyperglycemia acts as a key factor in the pathogenesis of DR [2, 3, 9].

This leads to activation of a cascade of events that, without treatment, culminates in the accumulation of fluids in the extravascular space, ischemia, proliferation of abnormal vessels, and blindness [9, 33].

In DR, the first histological changes occur at the level of the retinal capillaries with basement membrane thickening, loss of pericytes, and change of the tight junctions. This leads to loss of the inner blood-retinal barrier incompetence, promoting vascular hyperpermeability, and vaso-occlusive phenomena [9, 33, 34].

At present, the research focuses on the identification of molecular and biochemical mechanisms that contribute to the changes described above [9].

Several potential biochemical mechanisms have been implicated and activated by chronic hyperglycemia, polyols [9, 35–38], the accumulation of advanced glycation products (AGE) [9, 35, 37, 39–42], activation of protein kinase C (PKC) [9, 35, 43], and leukostasis [9, 34, 35]. These channels promote oxidative stress [33, 44], vascular dysfunction, and the emergence of pro-inflammatory cytokines, such as the vascular endothelial growth factor (VEGF) [9, 33, 34, 45], TNF α [9, 33], nitric oxide (NO) [9], prostacyclin [9], IGF-1 [9, 33], NF-*k*B [33], PlGF [9], and interleukins 1 and 6 [33]. Of these factors, VEGF has assumed a particular importance, having been identified in the vitreous and retina of individuals with DR [9, 45] and being considered as one of the main stimuli for DME and PDR [46].

VEGF is a potent mitogen of endothelial cells with a molecular weight of about 45 kD [46–48] and is one of the main cytokines expressed as a result of persisting hyperglycemia, resulting in pathologic angiogenesis, vascular permeability, and increased expression of pro-inflammatory cytokines [47, 48]. In this way, VEGF is also been targeted as a therapeutic tool in DR, with anti-VEGF drugs being considered the treatment of choice for DME, alone or in combination with corticosteroids and laser therapy [48].

Another mechanism discussed as responsible for edema in DR is related to the deregulation of the activity carrier of water molecules resulting from the retinal metabolic activity. This was carried out by the Muller cells, in particular, by the change in the activity of water channels (Aquaporin-AQP4) and potassium channels (Kir, Kir 2.1 4.1) with potassium accumulation in the cells of Muller and their hydration and retinal edema [49, 50], which can be reversed by corticosteroids [50].

There is some evidence that in the earliest stages of the disease, VEGF is the main factor implicated in the DME. However, with the evolution of the disease into later phases, DME becomes chronic. Other cytokines [51], in particular IL-1, IL-6, IL-8, IP-10 (protein interferon-inducible protein), and MCP-1 (monocyte chemoattractant protein), related to aggravation and chronicity of the inflammation, are considered responsible for the inadequate response of the anti-VEGF.

DR is the result of complex and multifactorial mechanisms that lead to edema and retinal neovascularization.

Classification of Diabetic Retinopathy and Diabetic Macular Edema

Clinical international classification/disease severity level of diabetic retinopathy (Diabetic Retinopathy GDRPG—Global Project Group 2002) is based on the dilated fundoscopic or color fundus photograph examination [52–54] (Tables 53.2 and 53.3).

Table 53.2 GDRPG—global diabetic retinopathy project group 2002 classification of diabetic retinopathy (DR)

Proposed disease severity level	Findings observable
No apparent retinopathy	No abnormalities
Mild non-proliferative DR	Microaneurysms only
Moderate non-proliferative DR	More than just microaneurysms but less than severe NPDR
Severe non-proliferative DR (if instead of "or" if "and" could be considered very severe non-proliferative DR)	Any of the following: – More than 20 intraretinal hemorrhages in each of the four quadrants – Venous anomalies (venous beading) in two or more quadrants – Intraretinal abnormalities (IRMA) in at least one quadrant No signs of proliferative retinopathy
Proliferative DR	– Neovascularization – Vitreous/preretinal hemorrhage
The Portuguese Retina Study Group believes that any PDR should be subclassified according to gravity as follows [51]:	
Low-risk PDR	Neovascularization in or within 1 DD of the disc (NVD) with area <1/3 of DD or NV beyond 1 DD of the disc (NVE) with an area <0.5 DD
High-risk PDR	Neovascularization in or within 1 DD of the disc (NVD) with area ≥1/3 of DD or NV beyond 1 DD of the disc (NVE) with area ≥0.5DD or any NVD with vitreous hemorrhage
PDR with advanced diabetic eye disease	Any of the following: • Vitreous/preretinal hemorrhage • Rubeosis iridis • Tractional retinal detachment • Fibrovascular proliferation with traction

Table 53.3 GDRPG—diabetic retinopathy global project group 2002 classification of EMD. DD means diameter optic disc

Proposed disease severity level	Findings observable
Macular edema apparently absent	No retinal thickening or hard exudates in the posterior pole
Macular edema apparently present	Retinal thickening or hard exudates in the posterior pole
If macular edema is present, it can be further classified as follows:	
Mild: some retinal thickening or hard exudates in the posterior pole but distant from the center of the macula	
Moderate: retinal thickening or hard exudates approaching the center of the macula but not involving the center	
Severe: retinal thickening or hard exudates involving the center of the macula	

ESASO Classification of Diabetic Maculopathy

An OCT-based classification of diabetic maculopathy has recently been proposed by ESASO (European School of Advanced Studies in Ophthalmology). It includes seven qualitative and quantitative features, scored according to a grading system: central sub-foveal thickness, intraretinal cysts size, status of ellipsoid zone and external limiting membrane, disorganization of the inner retinal layers (DRIL), presence of hyperreflective foci, and presence of subretinal fluid and vitreoretinal relationship. The maculopathy is classified in four different stages, which reflect progressive severity of the disease: early, advanced, severe, and atrophic maculopathy. Some of these OCT parameters could also have prognostic value, such as the DRIL and alteration of ellipsoid zone which are predictors of poor treatment response, and subretinal fluid and hyperreflective foci which are considered inflammation biomarkers [55]. However, this classification based on OCT structural features does not take in consideration the hard exudates and lipoprotein plaques as a signal of chronicity and bad prognosis for visual function nor visual acuity per se, as prognostic and therapeutic biomarkers.

Current Treatment of Diabetic Retinopathy

To address the issue of the treatment, we need to consider both the severity of the disease and the importance of early diagnosis and treatment.

We must take into account that DR can present with different severity levels, depending on the time of evolution of the disease and, as recently shown [28], the subgroup of diabetes. The level of severity is essential to plan the level and complexity of the intervention. In this way, we can adequately plan and allocate human and financial resources according to the level and complexity of each case [56] (Fig. 53.1).

On the other hand, a screening program for early detection and treatment allows an earlier intervention. It has been estimated that only 10% of resource consumption is needed at this time, instead of what would be required in the advanced stages of the disease and with very encouraging results [56]. Preferably, early detection and treatment programs must be carried out with a standard performance of proximity to the diabetic patient, including screening mobile units and use of telemedicine [56].

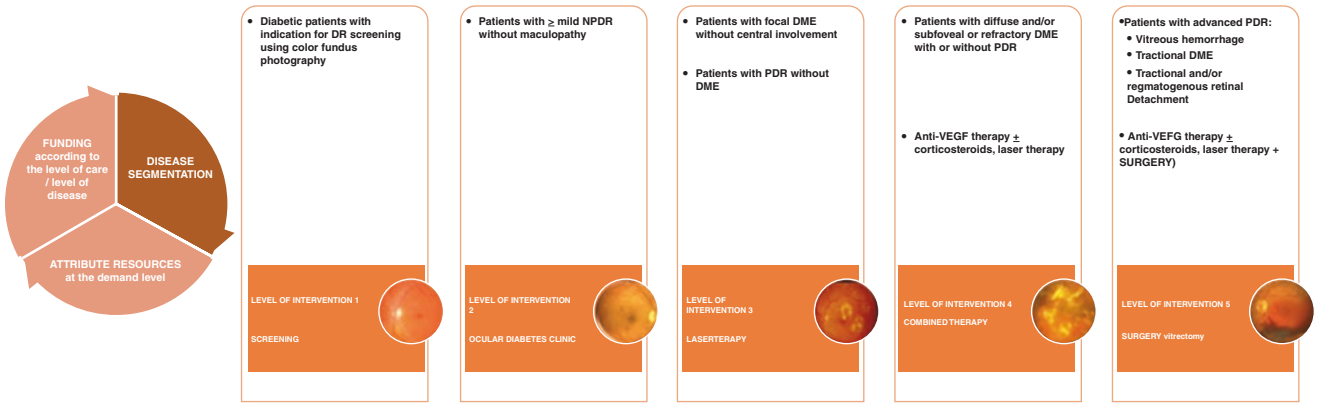

Fig. 53.1 DR levels of intervention and their relevance in health planning. We defined five levels of disease according to the level of severity. Each level of disease corresponds to a level of care. Note that there is an increase in complexity as the level of disease increases

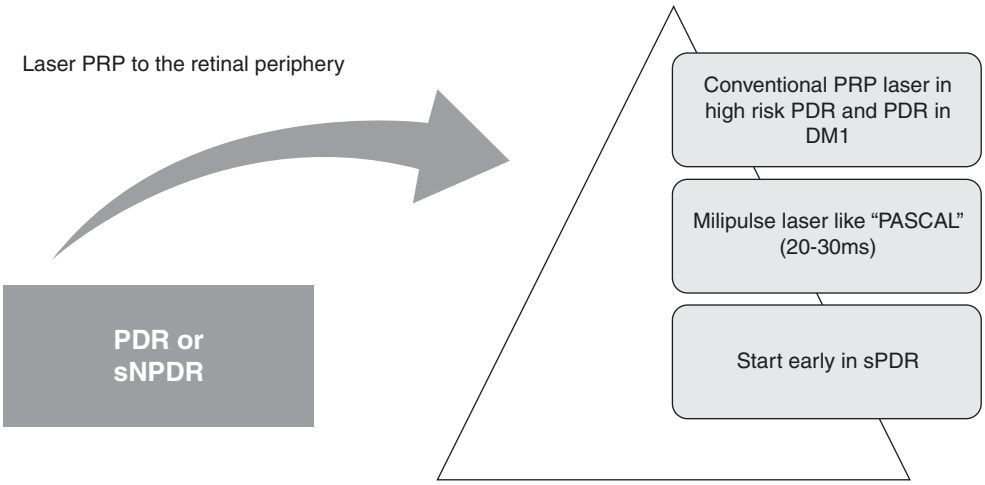

Fig. 53.2 Laser therapy for PDR. Conventional PRP laser should not be avoided in cases of high-risk PDR and PDR in type 1 DM patients. When using a multispot laser, treatment should be more intense so as to be equivalent to conventional PRP laser. Do not wait in severe PDR, particularly in patients with high-risk characteristics

It should be noted that, in each patient, DR can manifest with a predominantly ischemic or exudative component, sometimes mixed. In the first case, we are dealing with an evolution toward very severe NPDR or PDR. In this situation, although there are references to positive results with the use of anti-VEGF [57], the therapy of choice continues to be thermal laser. The treatment is carried out to the periphery of the retina, with the panretinal photocoagulation (PRP) [58] technique or more smoothly, with a technique called targeted retinal photocoagulation (TRP) using a multispot laser [59] (Fig. 53.2). The thermal laser, with a photocoagulation effect, has been a standard therapy of PDR [60] with very long-lasting results. Laser is truly recommended in contexts of low availability of resources, difficulty to follow patients, poor compliance, patients with reduced mobility, PDR in patients with type 1 diabetes, and advanced PDR where it is mostly combined with vitrectomy. In addition to being an effective treatment in the PDR, laser phototherapy has also been used as an efficient eye treatment procedure, thus preventing the onset of blindness due to hyperglycemic conditions [56, 61–63]. Advanced PDR with vitreous or preretinal hemorrhage and fibrovascular proliferation, particularly associated with retinal or macular detachment, are approached with surgical procedures—vitrectomy associated with intraoperative laser in a PRP pattern [56]. In this setting, a very early vitrectomy, with previous (2–3 days) anti-VEGF IV injection associated with endolaser PRP is an effective long-term treatment for PDR and vitreous hemorrhage.

The exudative component predominates in DME. Early stages of vascular edema, either focal or multifocal, do not imminently threaten fovea. In this case, the laser can still lead to better clinical outcomes [56, 61–63]. It should be emphasized that the laser treatment performed in the macular area follows the softer parameters and small spot diameter to avoid any damage to the microstructure of the macular retina.

It should be emphasized that a clear cut exists between center involving macular edema and other forms of DR with less severe edema [64]. The DRS and ETDRS trials [65, 66] in the 1970s showed that the results of laser photo-

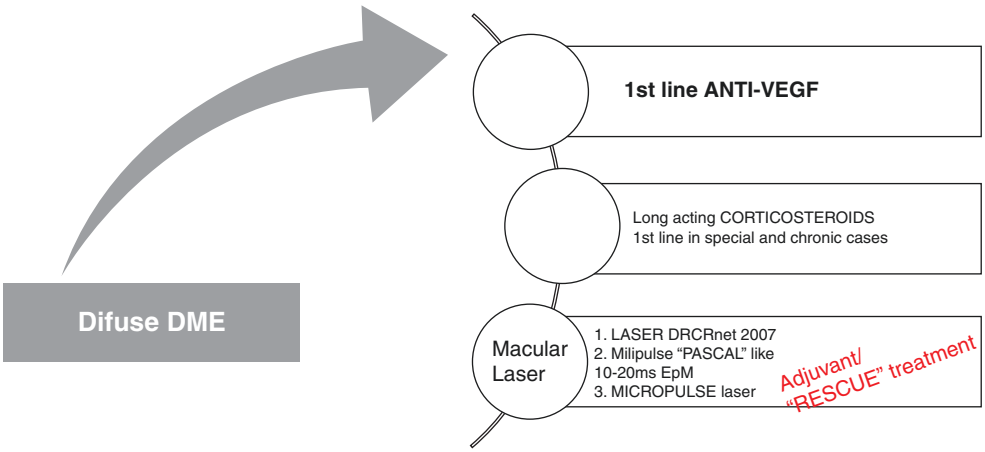

Fig. 53.3 Treatment options for diffuse DME: first line, anti-VEGF; second line, long-acting corticosteroids (eventually as first line in special and chronic cases); third line, which uses laser therapy at macular area for DME (with or without PRP at retinal periphery) as rescue or adjuvant therapy

therapy in DME were not encouraging [65, 66]. Only 3% of the treated patients had a gain of 15 ETDRS scale letters at the end of three years, and more than half continued to lose vision despite the laser monotherapy treatment [65]. Many of these patients presented with a diffused or subfoveal exudative component (diffuse DME) and with more advanced levels of disease. We can even say that the treatment paradigm of DR has changed, mainly for diffuse and advanced DME with large lipoprotein exudates, where anti-VEGF (bevacizumab, ranibizumab, aflibercept) [67, 68] therapy is now indicated as the first-line therapy (Fig. 53.3).

Indications for laser use as first line include the vasogenic subform which is clinically characterized by the presence of focally grouped MA and leaking capillaries [69], eyes affected by DME with CRT less than 300 μm [69], PEVAC-like lesions which requires the use of a milipulse low power laser [70], and eyes with persisting vitreomacular adhesion [67]. Subthreshold grid laser treatment can be helpful in eyes with better visual acuity affected by early diffuse DME, in order to avoid the collateral thermal diffusion and the consequent chorioretinal damage [69]. Deferring laser led to superior results, especially in eyes with BCVA at baseline lower than 69 letters [71]. Laser therapy can also be used as rescue after failure of anti-VEGF therapy [72].

Indications for anti-VEGF use as first line include concomitant presence of *neovascularization*, increased *intraocular pressure*, *young age* and the *presence of the lens* because corticosteroids are cataractogenic, *aphakic eye* or *iris-sustained anterior lens* due to possible migration of the device to anterior chamber, and consequent corneal edema. The absence of *inflammation biomarkers* such as subretinal fluid (SRF), hyperreflective retinal spots (HRS), and hard exudates points to the use of anti-VEGF as first line of treatment [64].

Indications for corticosteroids use as first line include *recent cardiovascular disease/recent arterial thromboembolic events*, *pregnancy*/breastfeeding, *noncompliance* or impossibility to return to treatment or follow-up visits, and *vitrectomized eyes.*

Combined therapy: thermal laser with VEGF and prolonged action steroids and surgery. However, the evidence gathered continues to support individualized and multifaceted approach to the patient with DR [73], in which the anti-VEGF agents can be used in combination with the reference treatments, such as corticosteroids [74] and laser phototherapy [68, 75], which act as an adjuvant factor and long-term stabilizer [76] (Fig. 53.4). Currently, the thermal laser with the techniques identified as retinal saving [56, 77, 78] can be combined with an anti-VEGF and/or sub-tenon or intravitreal triamcinolone [79, 80] or extended release devices of dexamethasone [81] or fluocinolone [82]. The last are particularly indicated in patients who have been vitrectomized [83] and as first line in patients with contraindications to anti-VEGF use.

This approach has been rationally demonstrated by enhanced efficacy in clinical trials [72, 84–87] and in better and more efficient management of a healthcare provider system. In about 40% of patients, the response to anti-VEGF monotherapy was not satisfactory [72], and it might make sense to change drug class, shifting for a prolonged action corticosteroid [82], and/or associate the laser treatment (and/or macular periphery) [56].

The combination of drugs appears to be a valid option in order to enhance their global beneficial effects. The different drugs and/or laser therapy act synergistically in the various mechanisms of action that cause edema. The gain in efficacy achieved by combining drugs can reduce the total number of required treatments, decrease the adverse effects of the individual drugs [76], and improve the therapeutic *burden* on the patients [56]. Treatment procedures like vitrectomy and phacoemulsification also go along well with the combination therapy.

The laser therapy, like the vitrectomy, acts as the stabilizing element of the retina in the long term. This has been dem-

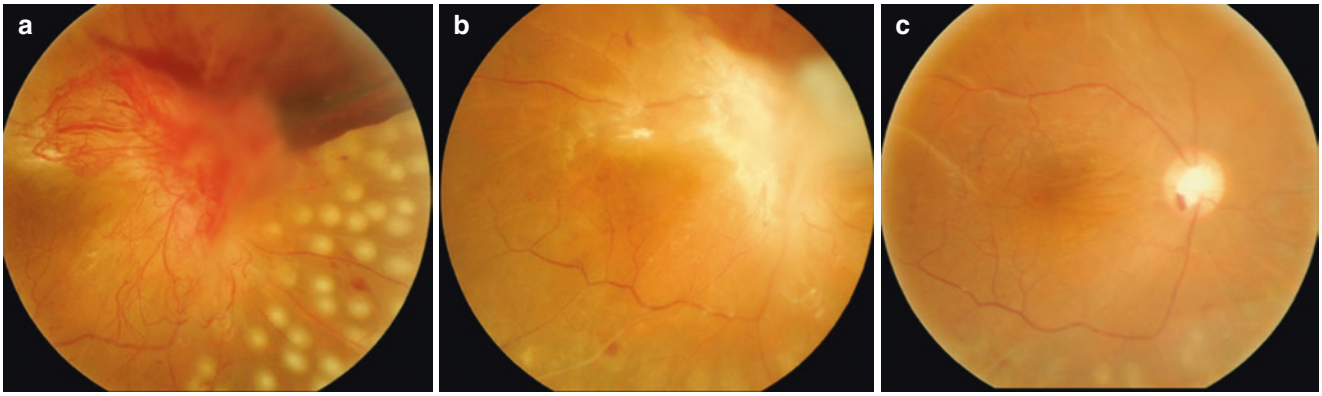

Fig. 53.4 Advanced PDR with vitreous and preretinal hemorrhage in a 35-year-old woman. (**a**) Laser photocoagulation was performed as there was optical transparency. (**b**) Two days after intravitreal ranibizumab injection: there was total regression of neovascularization and a fibrotic "shift" of fibrovascular tissue. (**c**) Two days after vitrectomy with "peeling" of the fibrovascular complex. The result was excellent with the maintenance of visual acuity of 0.8 due to early action in combining therapies. However, this was a highly resource-consuming procedure, which included laser, vitreoretinal surgery, anti-VEGF, and corticosteroids. The treatment could have been simpler by using fewer resources if it was held earlier before reaching advanced PDR

onstrated by the clinical stabilization achieved in laser-treated diabetic patients that lasts for decades.

In the near future, we will continue to use anti-VEGF as well as long-acting steroids in slow-release devices with the features of modulators of neovascularization and edema. The association of genetic therapy opened new frontiers, including the use of viral vectors for transfer of PEDF (pigment epithelium-derived factor) [88–90]. This cytokine has shown to have anti-inflammatory and antioxidant properties [91], as well as the ability to reduce capillary hyperpermeability and edema. The knowledge that laser phototherapy induces retinal environment modeling for production of chemical mediators [92], along with PEDF, either by activation of microglia or the call of medullary stem cells with repair functions, allowed us to further explore this therapy using the laser in earlier phases. Associate methods of improvement of metabolic control [12, 93] and neuroprotection [32] will be the major challenge in treating DM and DR. We anticipate a customized therapy for the individual patient, where the method of treatment will allow to maximize the results and have fewer side effects and fewer visits to the hospital, reducing the burden and treatment cost [93].

Ocular Manifestations of DM Other Than DR

As mentioned above, diabetic eye disease is not limited to DR, even though DR is the best-known microvascular complication (Table 53.4).

Other ocular manifestations of DM can be divided into vitreoretinal, when affecting the vitreous or retina such as the DR, or non-retinal, if they affect other ocular structures [18, 94].

Table 53.4 Ocular manifestations of DM other than DR

Ocular manifestations of DM other than DR	
Blepharitis	Non-arteritic ischemic optic neuropathy
Chalazion	Oculomotor nerve palsy
Dry eye	Asteroid hyalosis
Corneal ulcer	Retinal artery occlusion
Neurotrophic keratitis	Retinal vein occlusion
Loss of accommodation	Ocular ischemic syndrome
Refractive fluctuation of vision	Lipemia retinalis
Cataract	Diabetic papillopathy
Glaucoma	Pupillary abnormalities

Vitreoretinal Manifestations

These include the retinal arterial and venous occlusions and the ocular ischemic syndrome, conditions in which DM is a predisposing factor [18, 94].

The retinal vein occlusions correspond to the second most common vascular retinopathy after DR and are characterized by dilated and tortuous veins associated with intraretinal hemorrhages, cotton-wool spots (localized retinal ischemia), and macular edema. The central retinal vein occlusion involves the whole retina, occurring at the level of the optic disc, and the branch retinal occlusion involves a sector of the retina and is located usually at the level of pathological arteriovenous crossings [18].

The ocular ischemic syndrome (OIS) is a less frequent condition that results from chronic eye hypoperfusion due to significant stenosis/occlusion of the ipsilateral internal carotid or ophthalmic artery. Individuals with this pathology often have multiple systemic risk factors, which include DM, high blood pressure, and dyslipidemia. DM is even considered a major risk factor for carotid disease and consequently the OIS [18, 95].

The appearances of retinal emboli and the retinal arterial occlusions (RAO) are other complications that reflect multiple cardiovascular risk factors of diabetes, especially hypertension and dyslipidemia. The suspicion of an RAO is an ophthalmic emergency, and individuals should be immediately referred to a high-level ophthalmological care center. Symptoms include sudden and painless loss of vision [18]. Changes in the choroidal circulation have also been described [96].

Non-Retinal Manifestations

This group includes disease of eyelids and cornea, crystalline lens, glaucoma, and neuro-ophthalmic disorders.

Eyelids

Blepharitis (inflammation of the eyelids) and chalazion may be the first signs of DM [94].

Cornea

Diabetic patients exhibit reduced corneal sensitivity, resulting in a greater predisposition to infectious keratitis, neurotrophic ulcers, intolerance to contact lenses, erosions, and epithelial defects. There is also a slower healing of the corneal and structural changes in the hemidesmosome of the basal membrane, which leads to persistent epithelial defects even after a minor trauma. Corneal disease symptoms include pain, photophobia, and blurred vision, and the treatment usually consists of lubrication and therapeutic occlusion [18, 94].

Crystalline Lens

Refractive Error

Refractive fluctuation of vision can be a sign of DM and metabolic decompensation due to the change of the power of the lens diopter. This is due to the accumulation of sorbitol by increased activity of the enzyme aldose reductase, which leads to acute lenticular swelling that promotes a hypermetropic shift [94]. It is common when there is a sharp rise in hyperglycemia, often considered an inaugural symptom of DM.

Cataract

Cataracts are also an important cause of impaired vision in diabetic patients, with the risk of cataract increasing with the duration of DM and metabolic control [18]. Patients with type 1 diabetes can sometimes appear with a special type of cataract, a cortical snowflake cataract, which can be rapidly progressive [18]. In individuals with type 2 diabetes, there is worsening of the senile cataract and earlier appearance compared to nondiabetics [18]. Regarding cataract surgery, there are also particularities of DM: (1) preoperative macular edema can compromise visual recovery; (2) DR can rapidly worsen with surgery; (3) there is a prolonged healing time; (4) there is higher risk of postoperative inflammation and infection; and (5) there is higher risk of surgical complications [18, 94].

Glaucoma

Glaucoma is a progressive optic neuropathy, usually associated with increased intraocular pressure and changes in the optic disc and visual field [18].

Case-control trials show a relative risk of primary open-angle glaucoma of 1.6–4.7 in diabetics [18, 94]. DM also disturbs the short posterior ciliary artery self-regulation, exacerbating glaucoma optic neuropathy [18]. Also in DM, there is a greater risk of closed angle glaucoma due to an abnormally large crystalline. Moreover, a crisis of angle closure can also be a complication of an acute hyperglycemia crisis due to the abrupt lenticular edema [94]. Neovascular glaucoma is another type of glaucoma that can arise in diabetics. This type of secondary glaucoma is due to the neovascularization of the iris and angle induced by VEGF, whose production is stimulated by the ischemic retina. In a terminal phase, there is an obstruction of the aqueous humor drainage caused by the fibrovascular tissue in the trabecular meshwork and angle [94].

Neuro-Ophthalmic Disorders

Pupillary Abnormalities

Autonomic neuropathy leading to a denervation of the sphincter and pupillary dilator muscles can contribute to myopic pupils in scotopic conditions and an incomplete response to mydriatic agents [94].

Oculomotor Nerve Palsy

DM has been reported to be a cause of oculomotor palsy in 25–30% of individuals aged over 45 years [18, 94]. These are very common, usually isolated paresis of the III, IV, or VI pairs, and result from microvascular occlusion [18, 94]. Symptoms include binocular diplopia. Usually, there is a spontaneous recovery in 3 months, although recurrence may exist. The presence of other focal neurological signs must lead to the exclusion of compressive injury [18, 94].

Non-Arteritic Ischemic Optic Neuropathy

This condition results in anterior segment ischemia of the optic nerve, and it is estimated that 25% of people with this problem are diabetics [18].

There is an acute and painless decrease in visual acuity, with the presence of a relative afferent pupillary defect and optic disc edema [56]. There is no proven treatment, and the benefit of aspirin remains limited; but even without treatment,

this neuropathy usually remains stable [18]. The arteritic variant should be excluded with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and biopsy of the temporal artery due to its reserved prognosis and the need for urgent treatment with intravenous corticosteroids.

Conclusion

This chapter is a review focusing on ocular manifestations of DM, particularly DR, but not neglecting other lesser-known complications. We believe this matter is of particular relevance to the medical doctors who deal with diabetics, sensitizing them on the diabetic eye disease in order to promote a regular ophthalmologic evaluation and enable early detection of these visual debilitating changes.

We live in exciting times, with a constant innovation in prevention, diagnosis, and treatment of DR—the most important ocular complication of DM. However, more evidence with clinical trials on new therapies, clarifying their role, and the use of monotherapy or in combination are required. Other ocular and periocular structures, vessels, and nerves can also be affected by DM. The acquisition of knowledge regarding this issue enables us to diagnose and treat diabetes in a timely manner.Conflicts of InterestJosé Henriques declares having carried out consulting work for Novartis-Alcon, Bausch + Lomb, Bayer, Allergan, and Alimera.

Sara Vaz-Pereira declares having carried out consulting work for Bayer.

João Nascimento declares having carried out consulting work for Novartis, Bausch + Lomb, Alcon, Zeiss, and Bayer.

Marco Dutra Medeiros declares having carried out consulting work for Alcon, Allergan, Zeiss, and Bayer.

Susana Henriques has nothing to disclose.

Paulo Caldeira Rosa declares having carried out consulting work for Novartis, Alcon, and Bayer.

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Diabetes and Oral Health

54

Rosa Maria Díaz-Romero
and Manuel Salvador Robles-Andrade

Objective

- To provide healthcare personnel the necessary elements of the etiology, diagnosis, and treatment of disease in the oral cavity affecting people living with diabetes.
- Analyze systemic interaction models of periodontal disease and poor blood sugar control.

Introduction

For decades, oral health has not been considered among the priorities of government and international organization agendas, perhaps because most of the time poor oral health has affected morbidity and not mortality. Recently, there has been greater awareness from government organizations and even from the population that oral health is part of a person's general well-being. Also, more comprehensive studies have indicated that oral infections constitute a risk factor that generate or increase harmful health events in individuals. This change started in 2000 with the report of the US Surgeon General that was continued in 2002 in the Oral Health Program of the World Health Organization [1] that approved the resolution that urges the inclusion of oral health in chronic disease prevention programs. That is why we are interested in including this work in this chapter. We will provide the main concepts of the dentistry field to the entire multidisciplinary team allowing them to include this component in the comprehensive care of the diabetic patient.

We will start by stating how oral health affects quality of life. We will explain the interaction models of periodontal disease when blood sugar levels are uncontrolled. We will analyze how caries affect the teeth of diabetic people, as well as the repercussions of hyposalivation in the generation of swallowing disorders. We will present how the dentist and/or the periodontist diagnose an oral condition and the different phases that constitute periodontal treatment.

This chapter includes the protocol of diabetic care in the dental office with a clinical guideline followed by the physician, the dietitian, the endocrinologist, the nurse, and the diabetes educator, to detect an oral disease. We will also present the recommendations for the use of antibiotics and antimicrobial prophylaxis useful for the dentist.

Recently, there has been greater awareness that oral health is part of a person's general well-being with more in-depth studies of how oral infections constitute a risk factor for health in general.

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Oral Health and Quality of Life

Oral health is an essential component of good overall health and it is also a basic human right. According to the World Health Organization (WHO) [1], oral diseases have a significant impact in individuals and in society due to the pain these cause, leading to a decreased function and quality of life. The effects of oral diseases are considerable and expensive; it is estimated that treatment represents between 5% and 10% of the health expense in industrialized countries and it is above the resources of many developing countries.

Poor oral health can have severe repercussions in overall health; in the document *Vision 2020 of the International Dental Federation* in 2016 [2], it is stated that pain, dental abscesses, mastication problems, tooth loss, and pigmented or damaged teeth have significant effects in life and in the daily well-being of people. Some of these manifestations can even increase the risk of poor blood sugar control in people living with diabetes. The preservation of oral health is part of the comprehensive well-being of people with diabetes.

Oral health is a basic human right and its contribution is essential for good quality of life. Oral health is an essential component of good health.

Box 54.1
It is important for the multidisciplinary team involved in the care of diabetic patients, to be aware of the most important elements the dentist uses to diagnose and provide dental treatment to patients with diabetes.

Periodontal Disease and Systemic Interaction Models

Periodontal Disease and Systemic Interaction Models

The periodontium is a group of tissues that support the tooth, and it is made up of bone, periodontal ligament, radicular cementum, and gingiva. The only visible periodontal tissue is the gingiva that in normal healthy conditions the color is salmon, pink, or coral pink with variations that can be due to the degree of keratinization or to melanic pigmentations; these pigmentations are observed more frequently in Black patients. The external gingival portion is made up of a stratified keratinized epithelium that is firmly attached to a dense base of connective gingival tissue whose main function is to protect the underlying periodontal tissue from external stimuli; this epithelium continues to the gingival groove margin that extends from the crest of the gingival margin to the junctional epithelium; the latter maintains direct attachment to the surface of the tooth [3]. The most frequent periodontal disorders are due to the formation of a bacterial biofilm on the tooth surface; once the biofilm comes into contact with the sulcular epithelium at the level of the gingival margin, an inflammatory response begins in the underlying connective tissue that in 3–4 days becomes powerful enough to begin the destruction of connective tissue, losing up to 70% of the collagen within the inflammatory focus [4]. The clinical manifestation of the interaction between the bacterial biofilm that colonizes the tooth surface and that is in contact with the sulcular epithelium (Fig. 54.1) and the junctional epithelium is called periodontal disease; this term encompasses the two main infections that affect the tooth's supporting tissue: gingivitis and periodontitis.

Gingivitis is an inflammatory process that only affects the gingiva, and it is associated with the accumulation of bacte-

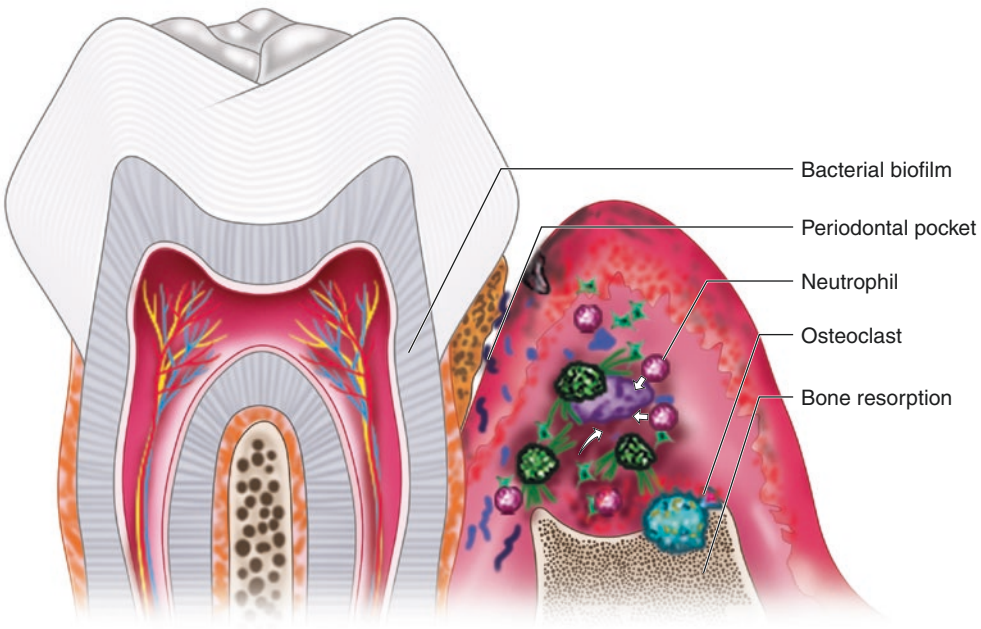

Fig. 54.1 Interaction between the bacterial biofilm and the sulcular and junctional epithelium. The progression of gingivitis to periodontitis involves the proliferation of epithelial cells apically throughout the radicular surface forming periodontal pockets; as these progress, the inflammatory infiltrate increases, starting the bone destruction

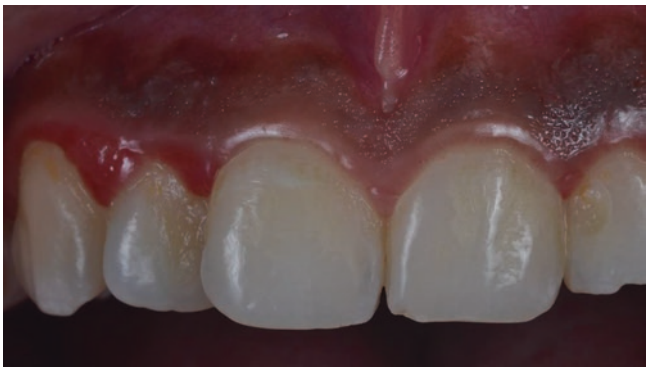

Fig. 54.2 Gingivitis. There is swelling of the gingival margin; it looks erythematous, associated with deposits of bacterial plaque on the teeth

Table 54.1 Strategies suggested to patients for personal plaque control [7]

Strategy	Justification
Teeth brushing at least twice a day	Patients who brush with this frequency keep their teeth for a longer period of time
Use of dental floss once a day	It significantly reduces gingivitis compared to only brushing
Routine use of toothpaste containing triclosan/copolymer	These are more effective in reducing bacterial plaque and gingivitis compared to fluoridated toothpastes
Routine use of mouthwash containing essential oils is suggested	These are effective in reducing bacterial plaque and gingivitis, even in proximal areas

rial plaque on the dental surface; when the bacteria of the plaque interact with gingival tissue, there is an inflammatory response characterized by an increase in the volume of the gingival margin, a change in the gingival color that looks erythematous and gingival bleeding in the presence of a stimulus (Fig. 54.2) [5]; this infectious process is reversible once the bacterial plaque is removed mechanically with the implementation of personal plaque control (PPC) where patients are instructed to follow an appropriate brushing technique and daily use of dental floss to achieve resolution of the clinical picture a few days after the correct PPC [6] (Table 54.1).

Periodontitis represents the progression of gingivitis to a destructive infectious process associated with the microbiological change of the bacterial biofilm and with a proinflammatory response of the host [8, 9]; this interaction is responsible for the periodontal destruction that causes dental mobility and tooth loss, making this the second cause of tooth loss [10] (Figs. 54.3 and 54.4).

Depending on the individual's susceptibility, the progression of gingivitis to periodontitis may vary; it has been suggested that the progression takes more than 6 months [11, 12]. The main microorganisms associated with periodontitis are *P. gingivalis*, *T. forsythia*, and *T. denticola*; these microorganisms produce enzymes and toxins that damage periodontal tissue and trigger an

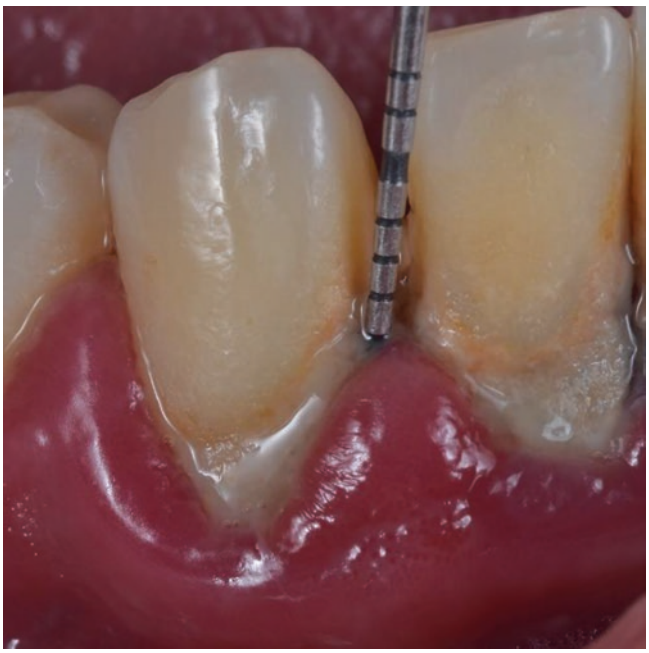

Fig. 54.3 Periodontal probing is a tool used to diagnose periodontitis. Under normal conditions, the probe penetrates the gingival groove 0.5–3 mm; in this case, the probe penetrates 5 mm, reflecting the presence of a periodontal pocket

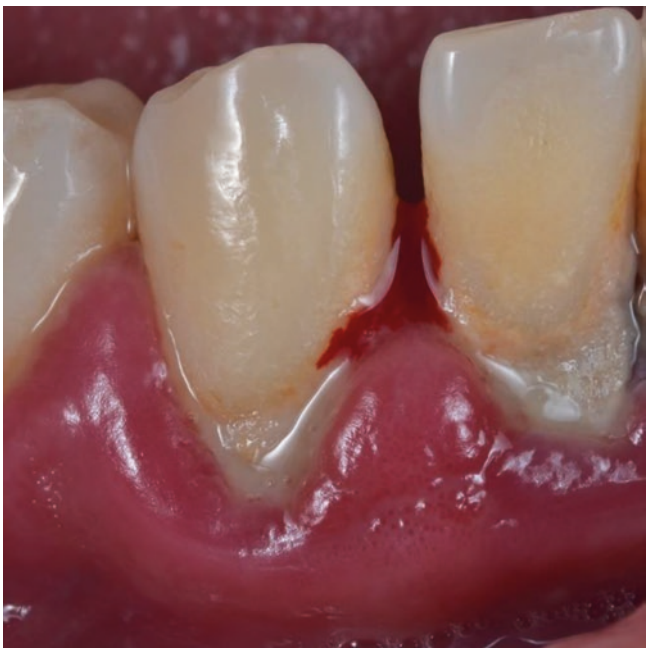

Fig. 54.4 When removing the periodontal probe, we observe bleeding, suggesting an active infection

inflammatory response. Once the inflammatory response is triggered, the red blood cells, fibroblasts, and structural cells of periodontal tissue release proteases, cytokines, and prostaglandins [13]. Proteases degrade collagen fibers

giving way to more inflammatory infiltrate. While the connective tissue is destroyed, epithelial cells proliferate apically throughout the radicular surface forming periodontal pockets; as these progress, the inflammatory infiltrate increases, starting the bone destruction mediated by osteocytes [14]. As more plaque accumulates, the microbial density increases, creating a chronic and more destructive response until the tooth is lost at some point [15]. The National Health and Nutrition Examination Survey (NHANES) reported that between 2009 and 2010, 47.2% of the American population over 30 years presented periodontitis [16]. The high prevalence of periodontitis represents a public health issue since it has been associated with a risk factor for the development of cardiovascular diseases [17, 18], to blood glucose control in diabetic patients, where the severity of periodontitis has a negative impact on glucose levels [19], on preterm birth and low birth weight, and on respiratory infections [20], among other chronic inflammatory diseases; furthermore, recently, it was observed that the severity of COVID-19 symptoms significantly increased in patients with poor oral health status and the recovery period was significantly delayed in those with poor oral health, while patients with good oral health had a faster recovery [21]. Among people with diabetes, periodontitis is associated with more diabetes complications. There is evidence that patients with periodontitis and with either type 1 or type 2 diabetes have significantly more renal complications and retinopathy [22].

Periodontal disease is considered as the sixth complication in diabetic patients; in the year 2000 [23], the American Academy of Periodontology stated that "the incidence of periodontitis increases among diabetic patients, increasing the frequency and severity in diabetics with more systemic complications" [24]; the increase in susceptibility is not related to the levels of dental plaque or to dental calculus [25]; collective evidence supports the relationship between both diseases, especially in poorly controlled diabetics [26, 27]. In an epidemiologic study carried out in the United States (NHANES III), individuals with poorly controlled diabetes have 2.9 times higher risk of developing periodontitis, compared to those without diabetes; on the other hand, those who controlled their diabetes properly did not experience any risk increase [28]. It has also been observed that in people with poorly controlled type 2 diabetes, the risk of alveolar bone loss was 11 times greater after 2 years, compared to nondiabetic control individuals [29]. This could be explained by the effect diabetes has in the changing adherence of neutrophils, in chemotaxis, and in phagocytosis that could favor bacterial persistence in the periodontal pocket increasing periodontal destruction significantly. The formation of advanced glycation end products, a key factor in many diabetic complications, is also produced in the periodontium, and its harmful effects over other organ systems may also be reflected in periodontal tissue [30]. Likewise, another study identified a 50% increase in the messenger RNA for the receptor of end products of advanced glycation in subgingival tissue of people with type 2 diabetes, compared to nondiabetic controls [31].

The systemic impact of periodontitis is due to the fact that the extension of the epithelium of periodontal pockets can reach 44–76 cm^2; if we put this into perspective, this represents infected tissue the size of the palm of our hand, having the ability to induce bacteremia and cytokinemia, inducing a low-grade systemic chronic inflammatory process [32]. These bacteremias are the result of mechanical stimulation of the periodontal pocket that became ulcerated during routine activities such as brushing or mastication, where not only do bacteria disseminate but also their products and endotoxins such as lipopolysaccharides [33]. Bacteria and bacterial antigens disseminated from periodontal tissue induce a systemic inflammatory response mediated by white blood cells, endothelial cells, and hepatocytes through the production of IL-1b, IL-6, TNF-a, and PGE2; with continued exposure in the systemic circulation, proinflammatory cytokines induce leukocytosis as well as the production of acute phase proteins such as CRP, fibrinogen, plasminogen, and complement proteins, among others [34, 35]. This bacterial and inflammatory mediator dissemination may have a significant impact on the metabolic condition of a diabetic patient; this is because systemic inflammation can start and disseminate insulin resistance. From an epidemiological standpoint, it has been observed that severe periodontitis is associated with an increase in HbA1C [36] in individuals diagnosed with T2DM [37]. On the other hand, in nondiabetic patients, progression of periodontitis has been associated with an increase in HbA1C and with carbohydrate intolerance; likewise, moderate and severe periodontitis has been linked to a greater risk of triggering diabetic complications like macroalbuminuria, kidney disease, atheroma plaque calcification, and cardio renal mortality [38].

In a systematic review of controlled clinical trials [39], we observed that when periodontal treatment is performed and periodontal infections are eradicated, the average reduction of HbA1C was 0.36%; one of the trials showed that periodontal treatment can even decrease HbA1C levels from 0.4% to 0.5%; this metabolic effect is similar to the one achieved when adding a second glucose-lowering drug to the therapy of diabetic patients [40].

Based on biological plausibility models, epidemiological and therapeutic evidence that link DM to periodontitis in a bidirectional manner (Table 54.2), it is imperative for the attending physician to promote oral health in diabetic patients, by requesting in all cases a consultation with the dentist.

Table 54.2 Evidence in the literature that supports a bidirectional relationship of periodontal disease and diabetes

Author	Key item
Eke PI, dye BA, Wei L, Thornton-Evans GO, Genco RJ	The National Health and Nutrition Survey (NHANES) reported that 47.2% of the American population over 30 years presented periodontitis between 2009 and 2010
Khader YS, Albashaireh ZS, Alomari MA	The high prevalence of periodontitis represents a public health issue. It has been associated with a risk factor for the development of cardiovascular diseases
Mealey BL, Rose LF	To blood glucose control in diabetic patients, where the severity of periodontitis has a negative impact on glucose levels
Haffajee AD. et al.	Periodontitis is a destructive infectious process linked to a microbiological shift in the bacterial biofilm and to a proinflammatory response of the host
Eke PI, et al.	The prevalence of periodontitis in the American population over 30 years is 47.2%
Kinane DF, et al.	Periodontitis has the ability to induce bacteremia and cytokinemia, inducing a low-grade chronic system inflammatory process
Löe H	Periodontitis has been considered the sixth complication of diabetes
Mealey BL, et al.	The severity of periodontitis has a negative impact on glucose levels
Engebretson S, et al.	When periodontal treatment is given and periodontal infections are eradicated, the average HbA1C reduction is 0.36%

The systematic impact periodontitis can have is because the extension of the epithelium of the periodontal pockets can go from 44 to 76 cm^2; in perspective, this represents infected tissue the size of the palm of our hand, having the ability to induce bacteremia and cytokinemia, inducing a low-grade chronic systemic inflammatory process.

Eradicated periodontitis can decrease levels of HbA1 from 0.4% to 0.5%; this metabolic effect is similar to the one achieved when adding a second glucose-lowering drug to the therapy of diabetic patients.

Based on biological plausibility models, the epidemiologic and therapeutic evidence that link DM bidirectionally to periodontitis, it is essential that the attending physician promotes oral health in diabetic patients, requesting an interconsultation in all cases with the dentist.

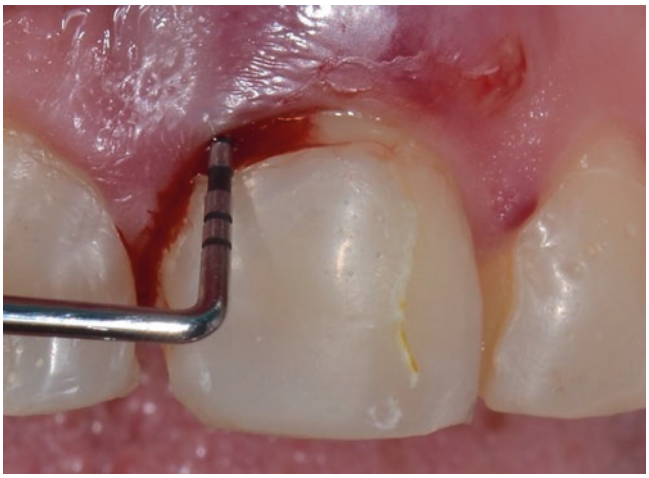

Fig. 54.5 Patient diagnosed with T2DM and periodontitis. We observe that the probe penetrates 9 mm; there is suppuration and bleeding, suggesting an active infection

Periodontal Diagnosis and Treatment

Diagnosis of periodontitis is clinical and based on the loss of clinical insertion levels, bony loss (Figs. 54.5 and 54.6), periodontal pocket depth, dental mobility, pathological dental migration, and signs of gingival inflammation (change in color, bleeding on probing, volume increase and exudate on probing) [7]. Overall, periodontal treatment is divided into three phases. In phase 1, therapy focuses on eliminating the causal agent (bacterial plaque), defective repairs that contribute to the retention of plaque are removed, and risk factors are controlled (such as smoking, diabetes mellitus, etc.). One of the most important aspects of periodontal phase 1 is providing patients instructions on personal control of bacterial plaque, instructing them on the proper use of dental floss, an appropriate brushing technique and the items that could facilitate proper oral hygiene [41]. It is absolutely essential to constantly assess the patient's personal plaque control since the long-term therapeutic success depends on it. Treatment of gingivitis consists of eliminating bacterial plaque through mechanical means; as was said before, one of its characteristics is that it is reversible once the bacterial plaque is removed; therefore, patients diagnosed with gingivitis only require periodontal phase 1 (Figs. 54.7 and 54.8).

Unlike gingivitis, periodontitis has an irreversible destructive pattern; in the most recent classification of periodontal diseases, glycemia in diabetic patients is used as an indicator of the rate of periodontitis progression [42]. Periodontitis has to be treated first with nonsurgical means like scaling and root planing, a treatment by means of which bacterial plaque and subgingival calculus are removed using curettes and ultrasonic instruments; on specific clinical scenarios, the use of antibiotics as well as mechanical treatment is necessary

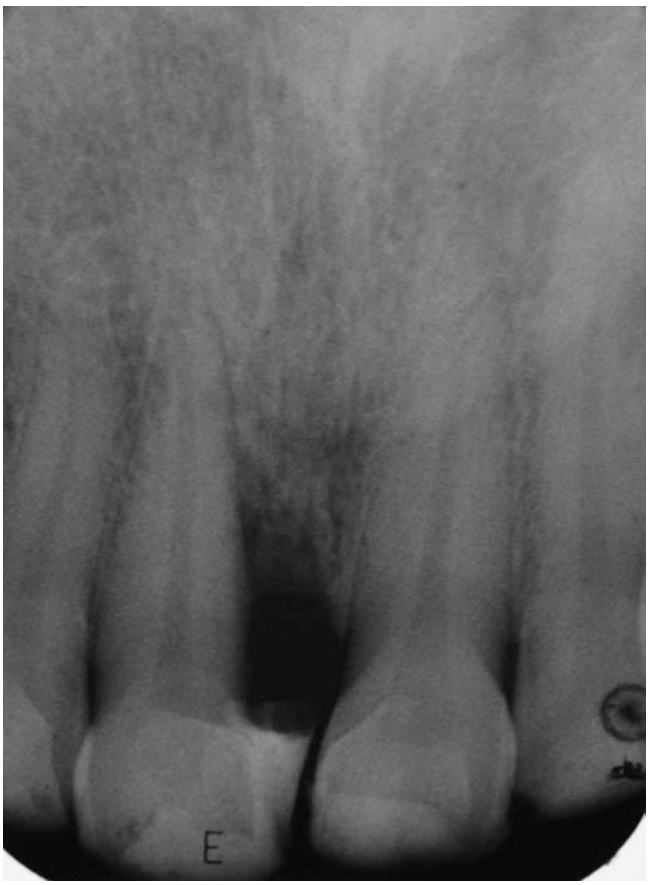

Fig. 54.6 X-ray corroborating the presence of vertical bony defect

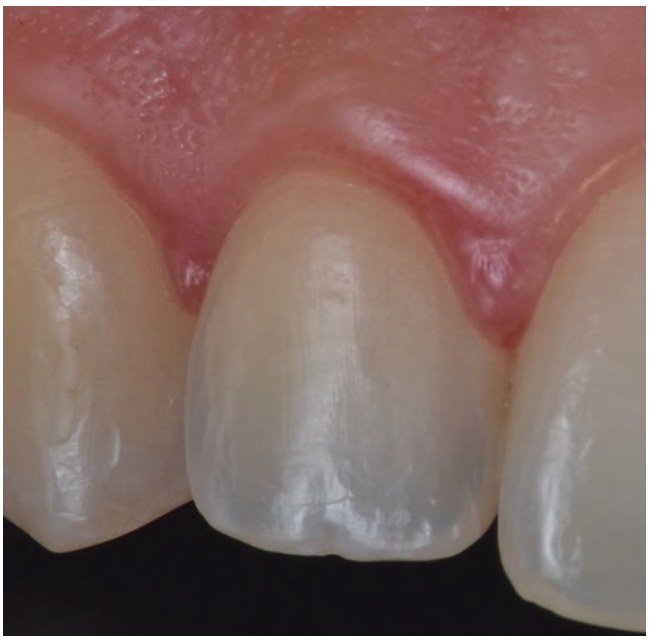

Fig. 54.7 Gingivitis. We observe increased volume of the gingival margin, with an erythematous aspect

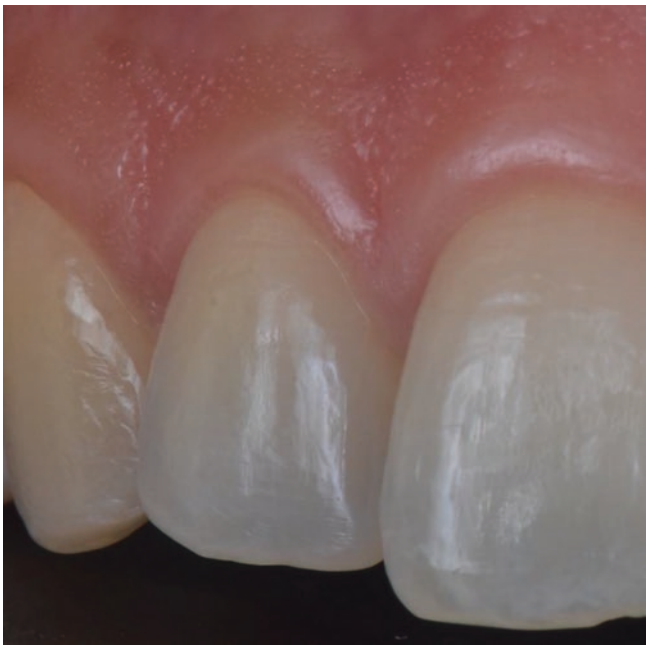

Fig. 54.8 After dental prophylaxis and correct oral hygiene instructions, we observe the resolution of the inflammatory process

[43]. If the periodontal pockets persist after the scaling and root planing, periodontal phase 2 is carried out; this is a surgical phase where a flap is lifted in order to perform a deeper periodontal debridement and therefore eliminate the infectious foci. In this phase, the periodontist can place biomaterials that stimulate the periodontal regenerative process [44].

Once the periodontal disease has been controlled, patients start the periodontal phase 3 or maintenance phase. In this phase, patients are reevaluated at 3–6-month intervals to identify if there is any site that has recurred; if so, it is treated at that moment, reinforcing the knowledge so that the patient can follow a good personal plaque control. The maintenance therapy should be carried out for the patient's whole life since the periodontitis can recur.

Periodontal treatment is divided into three phases. In phase 1 therapy which focuses on eliminating the causal agent (bacterial plaque), the defective repairs that contribute to the retention of plaque are removed, and risk factors are controlled (like smoking, diabetes mellitus, etc.). Periodontal phase 2 is a surgical phase where a flap is raised to perform a deeper periodontal debridement and thus eliminate the infectious foci. In phase 3 or maintenance phase, patients are reassessed in 3–6-month intervals to identify if there is a recurring site; if so, treatment is given at that moment and the knowledge is reinforced so that the patient can perform a proper personal plaque control.

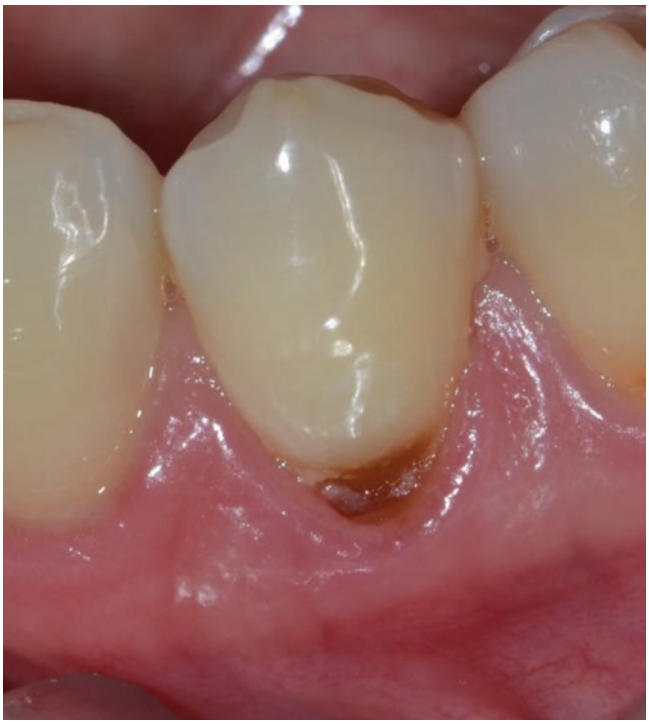

Fig. 54.9 Cervical caries in a diabetic patient

Dental Caries in Diabetics

According to the World Health Organization (WHO), dental caries can be defined as a pathological process characterized by a series of complex chemical and microbiological reactions that end up destroying the tooth. This destruction is the result of the action of acids produced by bacteria in the environment of the dental plaque. Clinically, a caries is characterized by a change in color, loss of transparency, and decalcification of the affected tissue. As the process advances, the tissue is destroyed and cavities are formed.

Throughout the world, around 60%–90% of school-age children and close to 100% of adults have dental caries, often accompanied by pain or a feeling of discomfort.

In diabetics, we observe cervical and atypical caries developed in areas that are not often affected in the rest of nondiabetic patients (Fig. 54.9); however, there is not a unanimous criteria on this theory.

Several reports support the increase in the caries index among diabetics, although there are others who point out a similar risk in nondiabetic patients. These discrepancies have been attributed to the inconsistent characteristics of the clinical evaluations performed, going from the use of several indices like decayed, lost, and filled teeth (CPOD) to bacteriological evaluations; other discrepancies come from the type of populations studied that go from children with type 1 diabetes to elderly patients with type 2 diabetes; however, it is a fact that glucose level in the saliva of nondiabetics is between 0.20 and 2.30 mg/dL, while in diabetics, it goes from 0.45 to 6.30 mg/DI [45]; this condition and the decreased saliva secretion are risk factors for the genesis of decaying processes. These factors alter saliva's buffering capacity that has an effect in the pH of bacterial plaque in teeth, and it affects the rate and the development of caries favoring the growth of microorganisms such as *Streptococcus mutans (Sm)* and *Lactobacillus acidophilus (Lb)* [46]. These are considered bacteriological indicators for their acidogenic and aciduric capacity; in fact, the quantification of these microorganisms has shown a correlation with the decaying process. Scientific evidence indicate that *Streptococcus mutans* is the microorganism associated with the onset of the lesion and *Lactobacillus acidophilus*, with the progression of the lesion; both bacteria are strong producers of acid; therefore, it is considered that the concentration level in saliva, in colony-forming units (CFU) of *Sm* and *Lb* (>105), is associated with intense cariogenic activity, and it is used as an indicator of the high content of fermentable carbohydrates in the oral media, an essential element for greater acidity and thus a greater risk factor. On the other hand, a diabetic patient often develops odontalgias with pulpitis, whose genesis is justified by the microangiopathic processes; the presence of these manifestations is a fact reported in the literature, as well as the repercussions that can cause the dissemination of microorganisms of the oral cavity to the rest of the body (CITA), with the generation of bacteremias that can be the initial factor to trigger generalized bacteremias that have led to death in diabetic patients.

Diabetic patients are more prone to infections; therefore, we have to take the following into account:

- Dental caries is an infection that as it progresses generates the formation of dental abscesses; therefore, this disease should be treated.
- Any dental abscess has to be treated actively to prevent dissemination of bacteria to the blood flow.
- Antibiotic coverage will depend on the type of intervention and the degree of control of diabetes. In some cases, to avoid complications, it is recommended to start preoperative and especially postoperative antibiotic coverage [47].

In diabetics, we observe cervical and atypical caries developed in areas that we do not often see in nondiabetic patients.

Dental caries is an infection that as it progresses generates the formation of dental abscesses; therefore, this disease should be treated. Any dental abscess has to be treated actively to prevent dissemination of bacteria to the blood flow.

Hyposalivation and Xerostomia

Another anomaly present in diabetics is xerostomia; according to some authors, this disorder is more exacerbated in females. This feeling of "dryness" is caused by the increase in diuresis and a decrease in the volume of extracellular fluid and to changes in the microcirculation of salivary glands that produce hyposialia; xerostomia is often accompanied by glossodynia, taste disorders, burning in the tongue, and halitosis; the decrease of salivary secretion favors the decrease of salivary pH and therefore cariogenic aciduric microorganisms like *Streptococcus mutans* and *Lactobacillus Acidophilus* which proliferate easily. The salivary flow rate is lower in diabetic patients; Screeby in Diabetes Care (1992) states that 63% of patients with T2D refer xerostomia; the authors of this chapter reported 35% [48].

The xerostomia observed in diabetic patients is not only conditioned by poor blood sugar control but also by changes in saliva composition (high protein and potassium content) and autonomic neuropathy that deteriorate glandular secretion.

Xerostomia is the subjective feeling of dryness in the mouth, a symptom reported by the patient. It can be the result of decreased salivary secretion or it can occur in the presence of normal salivary production. Xerostomia is present in 40–60% of diabetic patients who have poor control of the disease with very little salivary production stimulus from the parotid gland compared to patients who are capable of controlling the disease and normal subjects [49].

Hyposalivation in decompensated diabetic patients is explained by the increase in diuresis and polyuria that can affect the production of saliva.

On the other hand, since xerostomia is considered a subjective sensation of dry mouth, it may or may not be attributed to the decrease or interruption of the salivary gland function. Xerostomia not only causes psychological, social, and physical consequences; it also alters food swallowing (Figs. 54.10 and 54.11).

Xerostomia and hyposalivation can be manifestations present in patients with T1D with inappropriate blood glucose control. However, these manifestations can also be related to neuropathy [50].

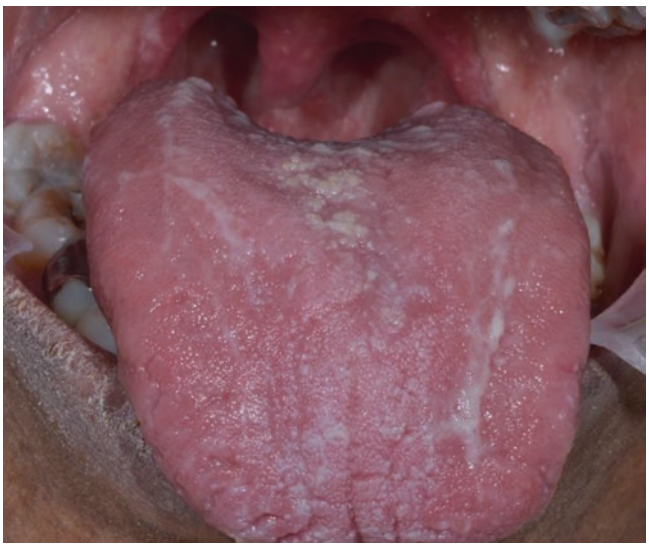

Fig. 54.10 Patient diagnosed with T2DM who presents xerostomia. Clinically, we can see a dehydrated oral mucosa, as well as thick saliva

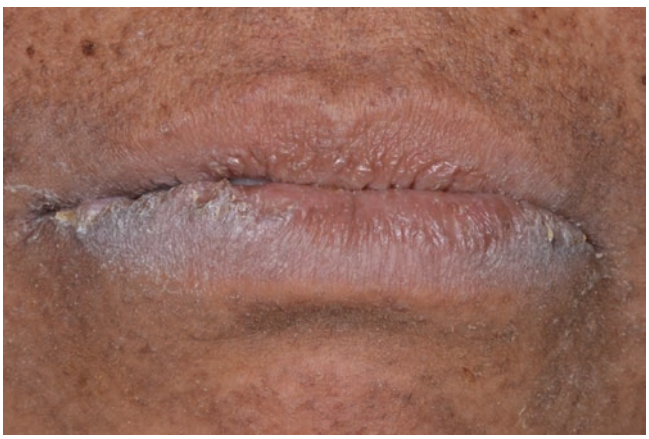

Fig. 54.11 The same patient where we see dehydration of the lip skin

Box 54.2
Xerostomia is a frequent oral condition that can affect oral functions as well as the patient's general well-being.

Box 54.3
Xerostomia in diabetic patients is not only conditioned by poor blood glucose control but also by the changes in saliva composition (high protein and potassium content) and autonomic neuropathy that will deteriorate glandular secretion.

Given its complexity, its treatment requires an interdisciplinary approach that should be focused on improving quality of life, decreasing possible complications, and promoting palliative care. Its etiology has been associated, among other factors, with the presence of systemic diseases including diabetes mellitus. The results of this systematic review and meta-analysis showed a global xerostomia prevalence of 42, 22% (CI of 95%: 33, 97%, and 50, 92%) in people with diabetes and a statistically significant association [51].

Frequent Mucosal Lesions in Diabetics

Candidiasis

Diabetics are prone to fungal infections; this is frequent in our setting. These are produced by the excess growth of *Candida* in the mouth, the digestive tract, the vagina, and other tissues. These are the skin—mucosa disorders that are sometimes systemic and produced by the *Candida* species (the most frequent type is *Candida albicans*). There are local factors such as smoking and the use of total dental prosthesis (Fig. 54.12) that can promote the appearance of candidiasis in the oral cavity as well as by extended periods of hyposalivation in uncontrolled diabetics.

Poor metabolic control is responsible for more fungal infections in diabetic patients than in the rest of the population since the glucose level in saliva acts as a substrate for *Candida*. Taking high doses of antibiotics or prolonged antibiotic use also increases the risk of oral candidiasis. Antibiotics destroy some of the healthy bacteria that prevent candida from proliferating too much.

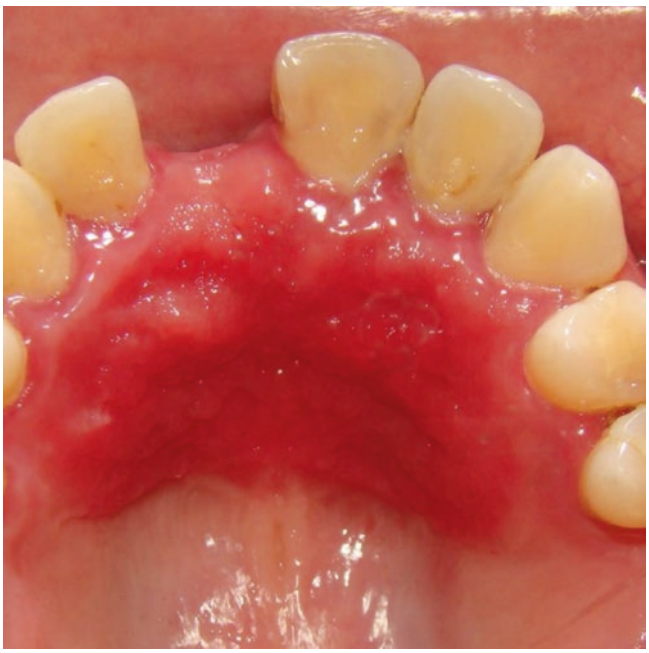

Fig. 54.12 Candidiasis associated with a movable prosthesis in a patient diagnosed with T2DM

Symptoms. Oral candidiasis appears as velvety whitish lesions in the mouth and tongue. Under this whitish material, there is reddish tissue that can bleed easily. Ulcers may increase slowly in number and size.

Exams and Tests. The physician or the dentist can often diagnose oral candidiasis by examining the mouth and tongue since ulcers have a distinctive appearance. If diagnosis is unclear, one of the following tests can be performed to look for candida organisms:

Culture of oral lesions.

Microscopic test of oral scrapings.

Treatment. For oral candidiasis in babies, treatment is often not necessary since it clears on its own after a couple of weeks. If it is a mild case of oral candidiasis after taking antibiotics, eating yoghurt or taking over-the-counter acidophilus capsules may help. The use a soft bristle tooth brush and rinse with a hydrogen peroxide water solution at 3% several times a day can help. Good control of blood sugar levels in people with diabetes can eliminate an oral candidiasis infection. The doctor can prescribe an antifungal mouthwash (nystatin) or chewable tablets (clotrimazole) if the oral candidiasis is severe or if there is a weakened immune system. These products are generally used for 5–10 days. If they do not work, other drugs can be prescribed [52].

Wound Healing and Changes in the Mucosa

Diabetic patients have impaired scarring. There are several theories that try to explain this phenomenon, like poor vascularization, decrease in platelet activity, or disorders in collagen synthesis [53]. Diabetes makes scarring or wounds slower and more difficult than normal. Diabetic patients not only have impaired scarring in acute wounds and slower closure of tissue making them more prone to chronic wounds. This is caused by an early inhibited or impaired inflammatory reaction and by a decrease in the ability to release growth factors and cytokines and the intercellular communication substances with several beneficial functions. When repair cell migration is interrupted, cell repair is hindered, thus decreasing the quality of the granulation status (scarring from the bottom to the top).

There is also diabetic microangiopathy present in the lower limbs, thus reducing the transport and repair capacity of tissue through the blood.

Diabetic patients often develop odontalgia with pulpitis; its genesis is justified by the microangiopathic processes, the frequent appearance of oral ulcers with a delay in wound healing, fissured tongue, and angular cheilitis; one of the most frequent and striking manifestations is reddening and atrophy of the mucosa.

Candidiasis is a frequent disorder in diabetics. Poor metabolic control is responsible for the fungal infections in diabetic patients more than in the rest of the population.

Healthcare Protocol of Diabetics in the Dental Office, Dental Management, Clinical History, and Patient's Level of Control

If we consider the statistics published by the WHO in 2014, the world prevalence of diabetes was 9% among adults over 18 years old. It is calculated that 1.5 million people died as a direct consequence of diabetes in 2012. More than 80% of the diabetes-related deaths were recorded in low- and medium-income countries.

According to WHO forecasts, diabetes will be the seventh cause of mortality in 2030; it is very likely that this type of diabetic patients will seek a dentist's consultation, and these patients may have an asymptomatic disease therefore going undiagnosed.

Clinical Management of Diabetic Patients in the Dental Office

It is very important for the dentist to be prepared to provide dental treatment to the diabetic patient. This includes an appropriate diagnosis of the prediabetic or the diabetic condition, as well as of the oral status of said patient. A full assessment should be performed including a medical and dental history, essential for an accurate diagnosis to create a treatment plan and to manage the patient's condition appropriately. It is important to specify the type of diabetes, the duration, the treatment modality, diet, exercise, oral drugs, or insulin (type and frequency of administration); patients who use insulin with a subcutaneous pump should be properly identified since they are often at risk of developing hypoglycemia since they have tighter control of the blood glucose levels.

Every dental office should have a glucose monitor, and the staff should be familiar with its use in order to measure the patient's capillary blood glucose (whether the patient has a diabetes mellitus diagnosis or not), before any procedure. However, sometimes it is recommended that the patients bring their own glucose monitor to the dental office if they have one at home, to avoid significant variations in the measurements. All the information on the blood glucose levels and HbA_{1C} should be included in the patient's medical record.

Practical recommendations are the following:

1. It is important to highlight the importance of preserving oral health in diabetics. Patients should be instructed on oral self-examination in front of a mirror and if they find an abnormal condition to consult the dentist.
2. What to do before the dental consultation? Blood glucose control should be at appropriate levels. The medication prescribed by the attending physician should not be suspended. When going to the dentist's office, bring a record of the last blood glucose measurements. Medication and therapies are used and information of the attending physician.
3. During the consultation, we must consider that stress causes changes in the body increasing the blood glucose levels. The dentist's consultation generates stress, as dentists are aware of that, so the consult is given early in the day and we recommend the patients no to change their diet or medication.
4. We highlight that the dentist will provide a detailed explanation of the patient's oral condition. He will perform prophylaxis and will instruct the patients on the use of oral hygiene instruments and will provide the next appointment. We recommend diabetic patients to visit the dentist every 4 months for a routine assessment and detection of possible infection foci.
5. If treatment is surgery, what to do before, during, and after the procedure are as follows: Before surgery, work with your dentist to create the safest surgery plan for you. Focus more on your diabetes control weeks before surgery. The dentist will examine and talk to you about your health. It is important to know all the drugs you are taking.
6. During surgery. You will see your dentist before surgery to discuss the control plan for your blood sugar during surgery.
7. After surgery. The dentist or the nursing staff will monitor your blood glucose level frequently. You may have more problems to control it if you have problems to eat, if you are stressed after surgery, or if you have pain or discomfort.

Be aware of signs of infection such as fever, an incision that is red or warm to the touch, swollen, more pain, or oozing. We recommend being prepared to call the dentist if any questions arise [54].

8. Diabetic patients should be informed that they are at greater risk of developing periodontitis, and if they develop it, blood glucose control will be more complicated having a greater risk of developing diabetes-associated complications like cardiovascular and kidney disease.
9. Patients diagnosed with T1DM, T2DM, or gestational diabetes should have a comprehensive oral examination that includes a periodontal assessment.

10. If periodontitis is diagnosed, it should be managed appropriately; if there is no periodontitis, the patient should follow a preventive program to monitor periodontal changes.
11. Diabetic patients who have extensive tooth loss should be encouraged to have dental rehabilitation in order to have proper mastication and nutrition. When patients loses all their teeth, intake of fibrous food becomes difficult, thus having to change to a softer food diet.
12. Annual oral exams are recommended in children and adolescents diagnosed with diabetes starting at age 6.
13. Patients who are not diagnosed with diabetes but who have obvious risk factors for T2DM and signs of periodontitis should be informed that they are at risk of developing diabetes; we suggest using a HbA1C test and refer them to the doctor for diagnosis.

Antibiotics and Antimicrobial Prophylaxis

The main objective of dental treatment is to eradicate infectious processes and then maintain dental and periodontal health. Controlled diabetic patients are treated the same way nondiabetic patients are; therefore, it is unnecessary to adjust the doses or modify the use of routine drugs in the dentist's consultation. It is important that before the consultation, patients continue their normal diet and their drugs according to the medical prescription. Emergencies and acute infectious processes (with a prior medical interconsultation) should be treated only in uncontrolled diabetic patients; routine treatments should be postponed until blood glucose levels are under control. It is important to consider the presence of organ damage (cardiomyopathy, kidney failure, cirrhosis, emphysema, or alcoholism) since special pharmacological considerations have to be given.

Antibiotics and Antimicrobial Prophylaxis

There is no scientific evidence to support that controlled diabetic patients are prone to postoperative infections when undergoing uncomplicated dentoalveolar surgery; therefore, it is not justified to prescribe antibiotics in these cases; however, if there is a picture of disseminated infection (fever, trismus, lymphadenitis, general discomfort, cellulitis), it is necessary to apply the principles of infection treatment (drainage, elimination of the etiological factor, empirical administration of antibiotics and reassessment).

Antibiotic prophylaxis should not be given routinely to diabetic patients (unless the patient presents another systemic condition that requires it). Routine treatments should be avoided in uncontrolled diabetic patients who have blood glucose levels greater than 250 mg/dL. If an emergency surgical procedure is necessary, appropriate antibiotic prophylaxis is warranted (even though there is no evidence to support it), following the same AHA principles to prevent infectious endocarditis (2 g of amoxicillin 1 h before the procedure). Infections in these patients should be treated aggressively regardless of blood glucose levels.

Guidelines the Physician Should be Aware of to Suspect an Oral Disease

Given that there is a high risk of developing periodontitis and other oral disorders, in a consensus carried out between the American Association of Periodontology and the European Federation of Periodontology on diabetes and periodontitis, the following clinical recommendations were made for physicians and other healthcare professionals:

1. Diabetic patients should be informed that they are at greater risk of developing periodontitis, and if they develop it, blood glucose control will be more complicated, thus making them at risk of developing complications associated with diabetes such as cardiovascular and kidney disease.
2. As part of the initial evaluation, patients diagnosed with T1DM, T2DM, or gestational diabetes should receive an oral and a periodontal examination.
3. Patients diagnosed with T1DM and T2DM should undergo an oral and a periodontal examination annually (even if they do not have an initial diagnosis of periodontitis).
4. Diabetic people who present clinical signs of periodontitis like tooth mobility, dental separation, or gingival oozing should receive immediate dental care.
5. Diabetic patients who present extensive tooth loss should be encouraged to undergo dental rehabilitation for proper mastication and adequate nutrition.
6. All diabetic patients should receive dental education.
7. We recommend oral examinations every year in children and adolescents diagnosed with diabetes starting at age 6.
8. Diabetic patients should be informed that they may present xerostomia and burning mouth and that they are at greater risk of developing candidiasis unlike nondiabetic patients.

Conclusions

Diabetes mellitus has a profound effect on the overall health of patients. Many clinical manifestations are seen in the oral cavity compromising quality of life. When infections are odontogenic, blood sugar control becomes difficult in these patients. That is why there should be a close relationship between the attending physician, the dentist, and other members of the interdisciplinary team who will provide specialized control of any risk factor that may influence the natural history of diabetes.

Concluding Remarks

- Oral health is an essential component of good health and it is a basic human right.
- Poor oral health can have severe repercussions in overall health.
- Periodontal disease is a highly prevalent infection that increases among diabetic patients.
- Periodontal disease increases the frequency and severity in diabetics with more systemic complications.
- Periodontal treatment can help to lower blood glucose levels.
- It is essential that the attending physician promotes oral health in diabetic patients.

Multiple Choice Questions

1. Do oral health and quality of life have any relationship in diabetic people?
   (a) Yes, because treatments constitute 5–10% of the health expense.
   (b) Only if patients do not control their blood glucose levels.
   (c) They do not have any relationship.
   (d) **Yes, because if the mouth is healthy, the person feels well.**
   (e) It depends on the type of diabetes.
2. How is the infectious process that affects support tissue of teeth and characterized by the destruction of teeth called?
   (a) Gingivitis
   (b) **Periodontitis**
   (c) Dental abscess
   (d) Gingival abscess
   (e) Periodontal abscess
3. It is one of the main bacteria associated with periodontitis.
   (a) *S. mutans*
   (b) *S. sanguis*
   (c) ***P. gingivalis***
   (d) *S. aureus*
   (e) *L. acidophilus*
4. Dental caries is an infection that as it advances it causes the formation of dental abscesses that should be treated in diabetics only when:
   (a) There is no blood sugar control.
   (b) **They should always be treated to avoid dissemination of bacteria.**
   (c) When purulent abscesses are formed and there is fever.
   (d) When they go to a specialized hospital.
   (e) They should not always be treated; it depends on the depth of the caries.
5. Diabetics are prone to fungal infections such as candidiasis for the following reasons:
   (a) Because the germ is opportunistic
   (b) Because they are immunosuppressed and they have blood glucose that serves as a substrate for candida
   (c) For smoking and having little saliva
   (d) From the effects of the drugs taken by diabetics
   (e) **Due to the poor blood sugar control, the hyposalivation and glucose in the saliva that serves as a substrate for candida**
6. Xerostomia is present in 40–60% of diabetic patients and the causes are:
   (a) The increase in diuresis and the presence of infection foci
   (b) The decreased platelet activity or the changes in the collagen synthesis
   (c) **The increase in diuresis and changes in the microcirculation of salivary glands**
   (d) The periodontal disease and cervical cavities present in the oral cavity
   (e) That diabetics are thirsty constantly
7. What is periodontal phase 1?
   (a) To perform surgical procedures to eradicate infectious foci
   (b) **To eliminate the causal agent in a nonsurgical manner and control risk factors**
   (c) To perform tooth cleaning
   (d) To use antibiotics to eliminate infectious foci
8. What is the effect of periodontal therapy in HbA1c levels?
   (a) They are maintained the same.
   (b) They increase after periodontal treatment.
   (c) They decrease but not significantly.
   (d) **They decrease up to 0.5.**
9. What do we recommended the diabetic patients do before, during, and after the dentist's consultation.
   (a) **Do not suspend medication for going to the dentist and have records of the attending physician and recent blood glucose levels.**
   (b) Have a dental card.
   (c) Have the attending physician's telephone number and all the prescriptions of drugs taken.
   (d) Take the last appointment of the day to avoid any stress.
   (e) Fast before the appointment without brushing their teeth so that the dentist can see the oral condition.
10. Diabetic patients should take prophylactic medication when they present infection in the oral cavity.
    (a) It is always necessary.
    (b) Never.
    (c) Only if they have type 1 diabetes.
    (d) Only elderly patients.

11. An inflammatory process associates to bacterial plaque characterized by an increase in gingival volume and bleeding on probing and is reversible when the bacterial plaque is eliminated.
    (a) Periodontitis
    (b) **Gingivitis**
    (c) Candidiasis
    (d) Linear gingival erythema
    (e) Periodontal abscess

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Renal Disease in Diabetes

55

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History

Urinary anomalies in diabetic patients have long been described; many long-standing historical documents refer, for example, to the characteristic sweet taste or smell in the urine of these population. The first description of renal anomalies in diabetic patients goes back to the 1700s, when Domenico Cotugno de Bari described proteinuria in this population [1]. In the next century, Claude Bernard found nephromegaly in diabetic kidneys in 1840 [2], and it was not until 1936 that Kimmelstiel and Wilson described nodular-fibrotic lesions in the glomeruli and diabetic nephropathy, a syndrome characterized by hypertension, proteinuria, and loss of kidney function. Later, in 1969, Harry Keen did a landmark discovery in diabetic nephropathy with the description of albuminuria in diabetic patients and established it as a surrogate for glomerular damage. With all the former discoveries, Mogensen et al. proposed the clinical picture of the natural history for diabetic nephropathy in 1983 [3]. As of today, Mogensen's sequence of diabetic nephropathy continues to be the accepted paradigm with some new features being considered.

Epidemiology of Diabetic Nephropathy

As it is widely known, diabetes has epidemic proportions with a global estimated prevalence of 8.3% in the 2014, corresponding to an approximate of 387 million people worldwide [4], and it is expected to increase to 592 millions of affected individuals by 2035 [5], likely a reflect of worldwide obesity pandemia. Another inherent partner of this world's expected increase in diabetes mellitus is diabetic kidney disease (DKD). For type 1 diabetes, DKD develops in approximately 30% of patients [6] and in about 40% of those with type 2 diabetes. Diabetic population, both types 1 and 2, account for 30–45% of chronic kidney disease (CKD) patients, but since DKD diagnosis is based on the presence of albuminuria as diagnostic criteria, DKD is probably more prevalent when ophthalmologic examination, estimated glomerular filtration rate, and kidney biopsies are included as additional diagnostic criteria.

Pathophysiology

Even though hyperglycemia plays a major role in the development of DKD, other mechanisms have been proposed [7]. Hemodynamic, metabolic, inflammatory pathways, autophagy, and enhanced sodium-glucose transporter-2 (SGLT-2) expression have also been involved in the DKD progression.

Hemodynamic Pathway

Renin-angiotensin-aldosterone system (RAAS) activation, mainly through angiotensin II and endothelin-1, produces a vasoconstriction effect on the efferent arteriole and leads to the widely known hyperfiltration phenomenon. Along with this hemodynamic effect, both molecules enhance mesangial cell hypertrophy and proliferation, extracellular matrix deposition, hypertension, endothelial dysfunction, inflammation, and fibrosis [8].

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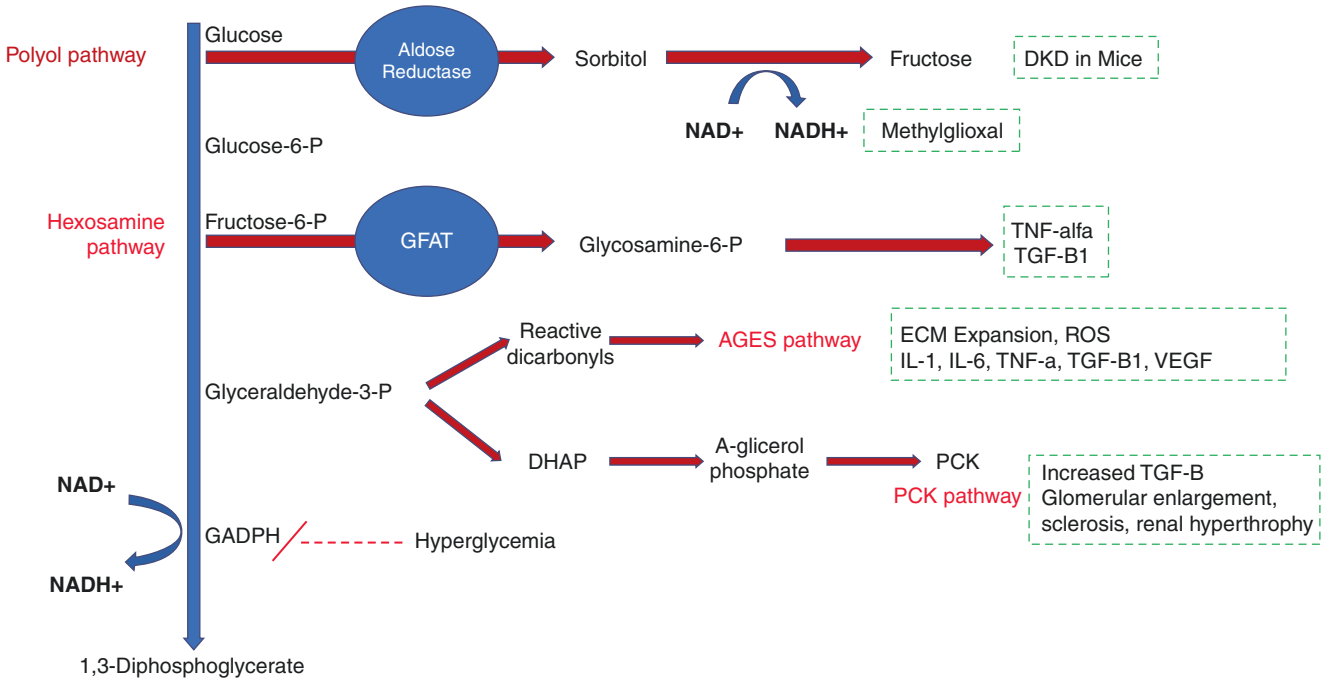

Fi. 55.1 Glycolysis in hyperglycemia. Glycolysis biochemistry is altered by hyperglycemia; it inhibits GADPH and increases upstream pathways, end products of such pathways

Metabolic Pathway

First described in 2001 by Brownlee [9], he showed that hyperglycemia activates superoxide, which inhibits glycolysis last enzymatic step at GADPH (glyceraldehyde-3-phosphate dehydrogenase) preventing formation of 1,3-diphosphoglycerate. The former increases upstream metabolic steps which end up in increased polyol pathway, hexosamine pathway, advanced products of advanced glycation end products (AGEs), and protein kinase C (PKC) (Fig. 55.1).

Polyol Path

Glucose is converted to sorbitol and into fructose afterward. Sorbitol production decreases intracellular NADPH, which ends up in less available glutathione that increases cellular stress and apoptosis. Oxidation of sorbitol leads to fructose generation, which increases NADPH to NAD proportion. This particular change enhances glycolysis inhibition by blockade of GADPH activity. Fructose generated by polyol pathway has shown to be nephrotoxic in mice models [8]; it increases glomerular and tubular damage along with proteinuria and decreases glomerular filtration rate (GFR).

Hexosamine Pathway

This track starts with fructose-6-phosphate which is then converted into glucosamine-6-phosphate, a transcription inducer of inflammatory cytokines such as tumor necrosis factor alpha (TNF-a) and transforming growth factor beta 1 (TGF-B1). The latter has well-known pathogenic effects such as mesangial matrix expansion and renal cell hypertrophy.

Advanced Glycation End Product (AGE) Pathway

AGE is a generic name for a group of products generated during hyperglycemia due to aberrant glycolysis. The process starts in glyceraldehyde-3-P and ends up in products such as glyoxal and methylglyoxal. These end products damage cells by impairing and/or modifying function of intra- and extracellular proteins, such as laminin and type IV collagen of the glomerular basal membrane (GBM), and increase permeability and thereby proteinuria [10–12]. Also AGEs increase the expression of profibrotic molecules such as fibronectin and collagen types I and IV, leading to extracellular matrix expansion. AGEs by themselves have the property of binding to pro-inflammatory receptors and induce expression of IL-1, IL-6, and TNF-a (tumoral growth factor alpha), TGF-B1 (transforming growth factor beta 1), connective tissue growth factor (CTGF), and vascular endothelial growth factor (VEGF) [11, 13–15].

Protein Kinase C Pathway

Similar to the AGEs, the protein kinase C pathway (PKC) metabolism begins with glyceraldehyde-3-P; hyperglycemia leads to dihydroxyacetone phosphate (DHAP) and ultimately diacylglycerol (DAG). This last element contributes to the activation of PKC, which in turn upregulates prostaglandin E2 and nitric oxide in the afferent arteriole leading to vasodilation and increases angiotensin II over the efferent

arteriole ending in vasoconstriction at this point. This vascular phenomenon increases glomerular pressure and corresponds to what is known as glomerular hyperfiltration [16–19]. PKC also mediates VEGF, leading to increased permeability of GBM, and induces CTGF and TFG-B1 which favor thickening of GBM and deposition of extracellular matrix [16].

Inflammatory Pathway

Chronically activated immune system and persistent low-grade inflammation in diabetes have been proposed as contributors to DKD. The latter through an inflammatory transcription factor, NF-kappa-beta (NFKB), is present in human kidney cells along glomerulus and tubule-interstitium. Hyperglycemia induces NFKB, which correlates with interstitial inflammation and proteinuria. Proteinuria by itself further enhances NFKB expression closing a positive feedback loop with hyperglycemia [20–25]. Inflammatory cytokines such as TNF-alpha, IL-1, IL-6, and IL-8 are much more expressed in renal tissue of diabetic models when compared to nondiabetic controls [26, 27]. Inflammatory cytokines correlate positively with the degree of albuminuria in diabetic patients. Also, contribution to GBM thickening, increase in endothelial permeability, apoptosis, and direct toxic effect to renal cells have been proposed as potential pathogenic mechanisms [7].

Autophagy

Autophagy is considered a protective phenomenon that allows cells to maintain homeostasis during starvation or oxidative stress [28, 29]. It allows cells to degradate intracellular proteins and organelles to self-sustain [29, 30]. Podocytes usually have a high level of autophagy. In vitro studies of podocyte exposure to hyperglycemia have shown impairment of this phenomenon and subsequent cellular injury [31–33].

SGLT-2

Hyperglycemia upregulates SGLT-2 in the kidney. This mechanism had been initially considered an evolutionary benefit for glucose claiming and energy storage; however, it has been now shown to have deleterious effects in diabetic patients by further contributing to hyperglycemic state and activation of all the physiopathologic pathways and autophagy impairment [34, 35].

Albuminuria

Emphasis on albuminuria across the scientific literature is explained by its correlation with the loss of glomerular filtration rate and increased cardiovascular risk [1, 2, 36]. Albuminuria is the consequence of a wide, and still not completely understood, interaction within functional (reversible) forces and histopathologic (irreversible) changes [37]. Functional forces are systemic and glomerular hemodynamic disturbances that lead the anatomical structures (glomerular basal membrane, podocyte, and mesangium) to develop irreversible changes. Nonetheless, neither is completely responsible for albuminuria. High hemodynamic pressure over non-damaged structures may not end up in albuminuria, as hemodynamic control over structurally damaged nephrons may not lead to albuminuria either. It has been proposed that the link that regulates interaction between the hemodynamic forces and anatomical structures is the endothelial glicocalix. Endothelial glycocalyx receives sheer stress, hypertension forces, hyperglycemia, and inflammation, among other factors, that ultimately end up in glicocalix degeneration and with it the loose of mechanical and electrical sieving that allows albuminuria.

Albuminuria is also the most sensitive screening tool to diagnose diabetic kidney disease. It is present in up to 55% of patients with DKD regardless of glomerular filtration rate. Only 13% of patients fulfill DKD diagnosis by albuminuria with decreased glomerular filtration rate and as little as 9% have only decreased glomerular filtration rate without albuminuria, as shown in the DEMAND Global [38].

Natural History of Diabetic Nephropathy: The Clinical Picture

From a clinical standpoint, DKD is the dynamic result of multiple risk factors divided as demographic (older age, gender, ethnicity), hereditary (family history for DKD, genetic conditions), systemic conditions (hyperglycemia, obesity, hypertension), kidney injuries (acute kidney injuries, toxins, smoking), and dietary factors (high protein intake). All the former leads to a sequence of susceptibility, initiation, and progression of DKD. The last two stages of this sequence (initiation and progression) correspond to the known and now changing natural history of DKD. Even though the description of DKD natural history involves mainly type 1 diabetics, it is widely accepted for both type 1 and 2 scenarios. A five-stage continuum through time is the result of two main variables, glomerular filtration rate (GFR) and albuminuria (Fig. 55.2).

Stage	Timeline	Histology	GFR	Baseline Albumin Excretion	Blood pressure	Reversible	Comments
I. Hyperfiltration	At diagnosis	Nephron hypertrophy	Increase 20 to 41%	Normal Excretion	Normal	Yes	Reversable
II. Silent Nephropathy	After 2 years	Increase in BM Mesangial Expantion	Increase 20 to 30%	Normal excretion	Normal	Structural Unknown Albuminuria Yes	Progress to clinically overt in 30-40% patients
III. Incipient Nephropathy	After 10-15 years	Not well defined	Increase 20 to 30%	Moderatly Increased	Incipient increase	Structural Unknown Albuminuria Yes	Manage risk factors
IV. Overt Nephropathy	After 15-20 years	Nodular sclerosis Capsular drops Arteriolar hyalinosis	Decline 1ml/month	Severe and progressive Increase	Hypertensive	No	Delay progression
V. End Stage Renal disease	After 25-30 years Final outcome	Glomerular global esclerosis	<15 ml/min	Slight decline	Hypertensive	No	Renal replacement

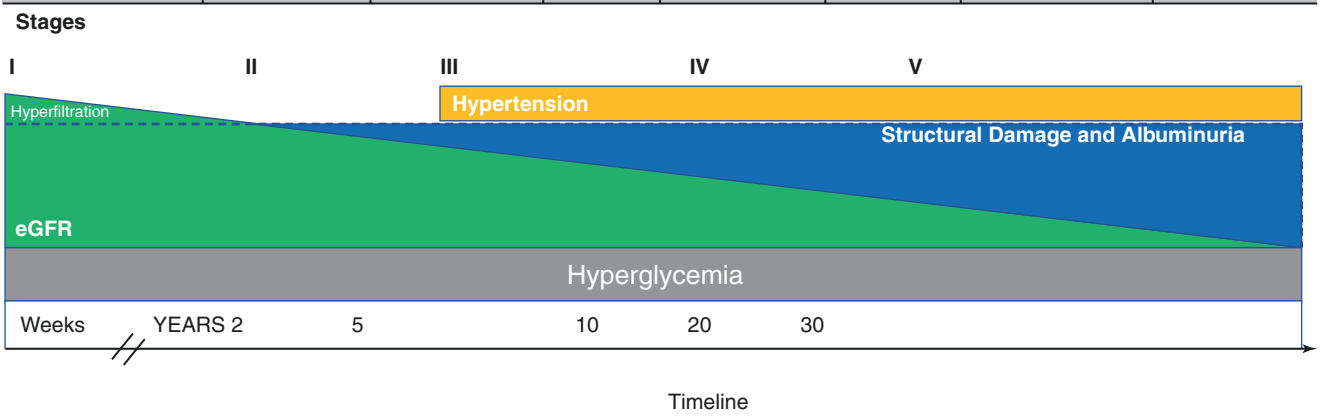

Fig. 55.2 Diabetic nephropathy. (Adapted and modified from Mogensen CE, Christensen CK, and Vittinghus E of the incipient diabetic nephropathy. 1983;32(June))

Early Hypertrophy and Hyperfunction (Hyperfiltration)

Structural, biochemical, and renal function changes are described. Within the structural anomalies, the most remarkable is the increased growth of both kidneys. Such phenomenon is a consequence of tubular hypertrophy and interstitial expansion related to SGLT-2 increased glucose reabsorption along with sodium and water. Hyperglycemia enhances nitric oxide, TFG-B1, CTGF, VEGF, and angiotensin II [1]. Such biochemical environment dilates the afferent arteriole and closes the efferent arteriole, leaving the glomerulus without appropriate autoregulation. The latter allows an elevated intra-glomerular pressure with an enforced 20–40% increase in GFR, a phenomenon known as renal hyperfiltration [2, 3]. Aside from hyperfiltration, dilation of afferent arteriole allows systemic arterial pressure to reflect directly on the glomerulus, further increasing glomerular stress and hyperfiltration effect.

All the abovementioned mechanisms are clinically silent since the main clinical features used to diagnose DKD (GFR and albuminuria) are absent at this stage. Nonetheless, when diabetic patients in this stage of nephropathy exercise with a $\geq$ 55% of the maximum expected heart rate (MEHR), they develop albuminuria. This is a lower threshold when compared to nondiabetic healthy individual, where $\geq$65% of MEHR is needed to start with some degree of albuminuria [3].

Up to this stage of nephropathy, hyperfiltration and exercise-induced albuminuria are reversible by glycemic control within 6 days [3], a fact that further emphasizes that kidney damage from diabetes comes from a long-standing process.

Silent Nephropathy (Glomerular Lesion Without Clinical Disease)

Diabetic patients remain in this stage for many years, without decrease in GFR of development of albuminuria in a steady state. Nonetheless, 30–40% of this group of patients will progress to overt diabetic nephropathy due to multiple histopathologic anomalies established through the glomeruli, tubule-interstitium, and blood vessels. Most remarkable modifications are thickening of the glomerular basal membrane, mesangial expansion, glomerulosclerosis, interstitial inflammation, and fibrosis [2].

Incipient Diabetic Nephropathy

Timeline for this stage corresponds to approximately 10–15 years of diabetic disease, and it is expected in about one-third of diabetic patients. The main characteristic of this phase is the onset and consistency of moderately increased albuminuria in the range between 30 and 300 mg/day. Likewise, steady increase of blood pressure adds on to the development of albuminuria at a rate of about 3 mmHg/year until overt hypertension is detected [2]. Type 1 diabetic patients with mild (<30 mg/day), moderate (30–300 mg/day), and severe (>300 mg/day) albuminuria have a prevalence of hypertension of 42%, 52%, and 79%, respectively. For type 2 diabetic patients, the same categories have a hypertension prevalence of 71%, 90%, and 93% [36].

When albuminuria is found within the first 5 years on new-onset diabetes in the absence of diabetic retinopathy and in the presence of nephrotic syndrome or accelerated loss of kidney function, a biopsy should be considered to rule out other causes of kidney disease other than diabetes.

Evolution of diabetic nephropathy up to this stage is most often accompanied by obesity, hyperuricemia, tobacco use, and noncontrolled hypertension. Treatment of the former entities along with glycemic control may lead to reverse albuminuria and its associated cardiovascular risk.

Overt Diabetic Nephropathy

This phase describes what it is now known as diabetic nephropathy syndrome: decreased GFR, increased proteinuria, and systemic hypertension. This stage's timeline is about 15–20 years after the diagnosis of diabetes mellitus and 30–40% of those who had diabetic renal involvement with progress up to this point. Structural and functional anomalies are irreversible, systemic hypertension is usually present and is the most damaging entity to kidney function, and there is a progressive decline of GFR at an approximate rate of 1 mL/min/month without medical treatment.

End-Stage Renal Failure

Within 25–30 years of diabetes mellitus evolution, end-stage renal disease is expected in those patients who had renal involvement. Clinical picture is not different from any other patient in this stage of kidney disease.

New Findings in the Natural History of Diabetic Nephropathy

The evolution of diabetic nephropathy has now changed. Most patients do not evolve without medical and pharmacological interventions seeking to control progression of disease. The most dramatic change in the natural history described by Mogensen et al. is the possibility to withhold progression of albuminuria from mild to moderate or severe and even when the former and the latter are established and achieve complete remission [39, 40]. Albuminuria evolution has changed since the widespread use of ACE inhibitors and ARBs; further body of knowledge is growing in the field of SGLT-2 receptor antagonists. Different phenotypes of diabetic nephropathy had been postulated, such as the non-albuminuric diabetic nephropathy (Fig. 55.3). However, despite the absence of albuminuria, some patients continue to lose GFR through time. The former evidence has led to new perspectives on the natural history of diabetic nephropathy in the light of comorbidities such as hypertension, obesity, ageing, and pharmacologic treatment. Four different phenotypes have been proposed [41]:

(a) Classical Diabetic Kidney Disease

This group fit into the classical natural history of diabetic kidney disease which resembles Mogensen's work the most, before generalized glucose-lowering and pressure-lowering treatments. Patients develop progressive glomerular hyperfiltration and a linear increment in albuminuria with a linear decline in glomerular filtration rate until kidney failure.

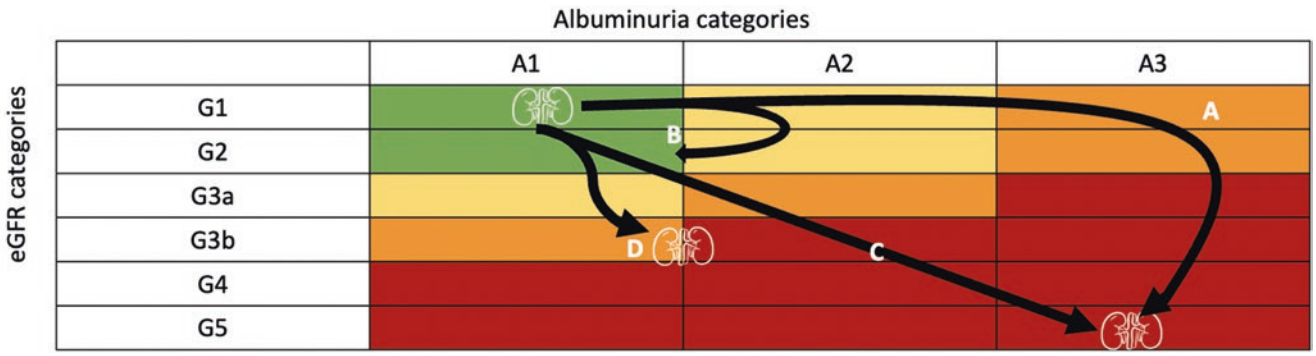

Fig. 55.3 New paradigm of diabetic nephropathy. Diabetic kidney disease trajectories. (**a**) Classic diabetic nephropathy. (**b**) Regression of albuminuria. (**c**) Rapid decliner. (**d**) Non-proteinuria/albuminuric DKD. (Adapted and modified from Oshima M, Shimizi M, Yamanouchi M. Trajectories of kidney function in diabetes: a clinicopathological update. Nat Rev. Neph. 2021)

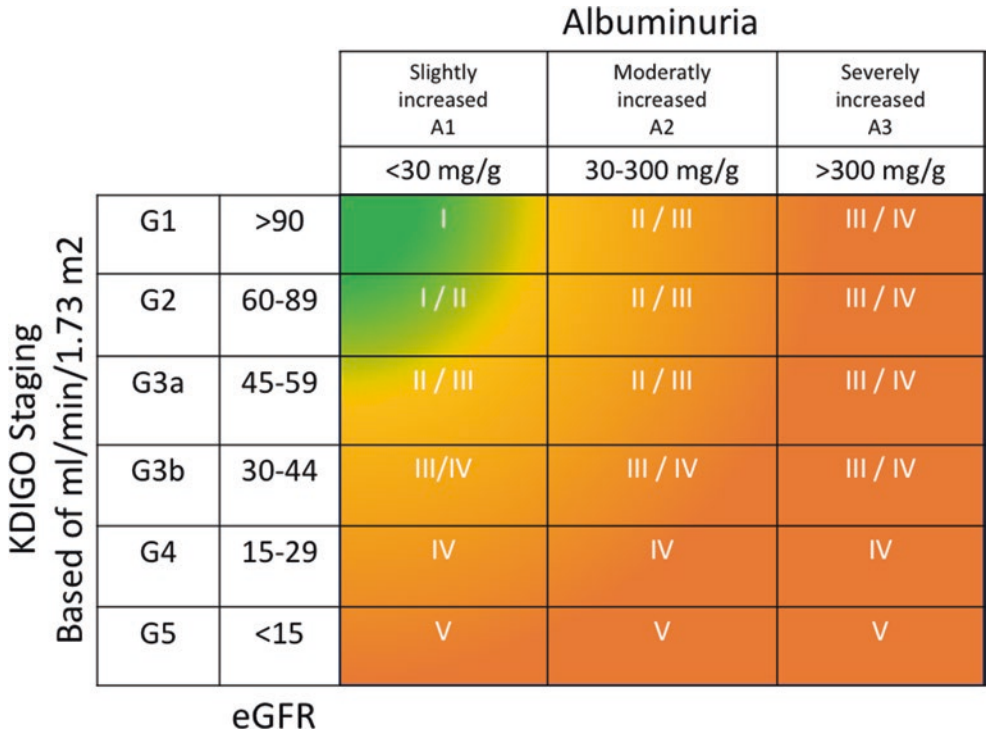

Fig. 55.4 Overlap between KDIGO CKD classification Mogensen's diabetic kidney disease natural history. M = Mogensen's classification stage. G = KDIGO CKD staging. A = Albuminuria. (Adapted and modified: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney inter., Suppl. 2013; 3: 1–150)

(b) Regression of Albuminuria

In the current era of generalized metabolic treatment, it has been shown in different populations that a switch and regression from moderate and severe albuminuria to normoalbuminuria may occur, with improvement of blood pressure and glycemia along with renin-angiotensin-aldosterone blockade and inhibition of sodium-glucose cotransporters. Different studies have shown a lower decline in glomerular filtration rate and lower progression to kidney failure and initiation of dialysis.

(c) Rapid Decliner

A rapid GFR decline is defined as a loss of ≥5 mL/min/1.73 m^2/year regardless of albuminuria degree. It has been hypothesized that this group may correspond to combined entities that coexist in the patient, such as tubulointerstitial diseases or a formerly damaged kidney on top of which DKD develops. Progression to kidney failure is develop in short period of time.

(d) Non-proteinuric/Non-albuminuric

The prevalence of this phenotype is around 20% for DM1 and up to 40% in DM2. Clinical characteristics for this group are female gender, hypertension, smoking, absence of diabetic retinopathy, and pharmacologic treatment with RAAS blockade. Also, a slower progression of GFR loss and kidney failure had been shown.

Natural History and KDIGO Classification

The KDIGO classification is the most widely used and accepted CKD classification. We propose an overlapping figure merging Mogensen's described natural history and KDIGO CKD progression (Fig. 55.4).

Nephropathology

Biopsy Adequacy

As for elemental histopathology recommendations, biopsy core should contain at least 12 full glomeruli. For light microscopy, tissue section must be within 2–3 micrometers thick; two slides must be assigned to H&E, two more for PAS stain, one for Masson trichrome, and one for Jone's silver methenamine. As for direct immunofluorescence, non-fixated tissue is recommended to perform frozen sections and incubate with immunoreactants: IgG, IgA, IgM, C1q, C3c, C4c, fibrinogen, albumin, kappa, and lambda. Finally, a small cortex fraction should be fixed in 2.5% glutaraldehyde for electron microscopy. This last technique is quite useful to characterize and differentiate within nondiabetic lesion on top of diabetic damage.

Histology

According to the Renal Pathology Society [40, 42], diabetic nephropathy is described by light microscopy, through four glomerular stages (Table 55.1); interstitial and vascular affections are also described (Table 55.2).

As for the mentioned stages and findings, we consider the following:

Table 55.1 Glomerular classification of diabetic nephropathy based on light microscopy

Class	Description	Criteria
I	Mild or nonspecific changes and EM-proven GBM thickening	Biopsy does not meet criteria for any other class below GMB in EM is >395 nm in females and > 430 nm in males[a]
IIa	Mild mesangial expansion	Biopsy does not meet criteria for classes III and IV Mild mesangial expansion in >25% of the observed mesangium
IIb	Severe mesangial expansion	Biopsy does not meet criteria for classes III and IV Severe mesangial expansion in >25% of the observed mesangium
III	Nodular sclerosis (Kimmelstiel-Wilson lesion)	Biopsy does not meet criteria for class IV At least one convincing Kimmelstiel-Wilson lesion
IV	Advanced diabetic glomerulosclerosis	Global glomerulosclerosis in >50% of glomeruli Lesion from classes I through III to be present

EM electron microscopy, *GBM* glomerular basal membrane
As described by Tervaert TWC, Mooyaart AL, Amann K, Cohen AH, Cook HT, and Drachenberg CB et al. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol. 2010;21 (4):556–63
aIndividuals to be 9 years old of age or older

Table 55.2 Interstitial and vascular lesions of diabetic nephropathy described by light microcopy

Lesion	Criteria	Score
Interstitial lesion	No IFTA	0
	<25% IFTA	1
	25–50% IFTA	2
	>50% IFTA	3
Interstitial inflammation	Absent	0
	Infiltration only in IFTA	1
	Infiltration outside IFTA	2
Vascular lesions		
Arterial hyalinosis	Absent	0
	A least one area of arteriolar hyalinosis	1
	More than one area of arteriolar hyalinosis	2
Presence of large vessel?	*Yes/no*	
Arteriolosclerosis (score by worst artery)	No intimal thickening	0
	Intimal thickening less than thickness of media	1
	Intimal thickening greater than thickness of media	2

As described by Tervaert TWC, Mooyaart AL, Amann K, Cohen AH, Cook HT, and Drachenberg CB et al. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol. 2010;21 (4):556–63

Stage 1. Early morphologic changes develop within the first 5 years of disease and affect glomerular basal membrane but can only be recognized at EM level. These findings correspond to simultaneous thickening and scarring of GBM, tertiary podocyte process effacement, and some focal podocytopenia. As diabetes continue to evolve, GBM accumulate type IV collagen, laminin, and fibronectin leading to double or triple length of its original width. The former thickening damages filtration barrier by direct endothelial damage and fenestral loss. Fibrin and fibrinogen begin to deposit in the subendothelium. At this point, first light microscopy findings are visible through PAS and Jones' methenamine stains, which reveal the important thickening of GBM. Simultaneously, microaneurysms and membrane remodeling as folding and laminated areas even focally duplicated membranes (Fig. 55.5).

Stage 2. After damage has been established at GMB, as a result of direct AGE effect, mesangium begins to accumulate extracellular matrix and leads to mesangiosclerosis. Early mesangiosclerosis is focal and involves only some glomerular segments; progression leads to global and diffuse mesangium replacement which end up in increased size and hyperlobulation.

Stage 3. Most characteristic diabetic kidney disease histologic findings correspond to this stage. Kimmelstiel-Wilson's nodular lesions are appreciated. These lesions are the result of diffuse mesangiosclerosis and microthrombi within the endothelium of dysfunctional microaneurysms. Microthrombi are constantly and chronically produced and reabsorbed, leading to collagen deposits in a laminated manner which finally generates a typical peripheral acellular nodule in the glomerular tuft. It is also common to find in former microaneurysm areas and foam appearance of endothelial and endocapillary cells. Such findings are known as "insudative lesions," a result of intracapillary pressure that manifests as "subcapsular drops," "fibrotic caps," and areas of hyalinosis, all of which share the same physiopathologic nature (Fig. 55.6).

Stage 4. Global sclerosis, nodular structures, and areas of hyalinosis characterize this stage. When more than 90% of the glomeruli present the mentioned findings, advanced interstitial fibrosis and tubular atrophy (IFTA), along with vascular damage, are common (Fig. 55.7). This is the final stage of cumulative damage and results not only of metabolic injury but also from chronic ischemia after vessels develop nodular hyalinosis, sclerosis, tunica media hypertrophy, and tunica intima fibrotic obliteration.

Nowadays, immunofluorescence and immunohistochemistry are considered as part of routine assessment of kidney biopsy (Fig. 55.8). As previously stated, 5 mm of non-fixed renal cortex is desirable for frozen cuts. If the latter is not feasible, the study can be performed from tissue out of the paraffin block, which even though is useful; it must be pointed out that such technique is less sensitive than frozen cuts without fixation.

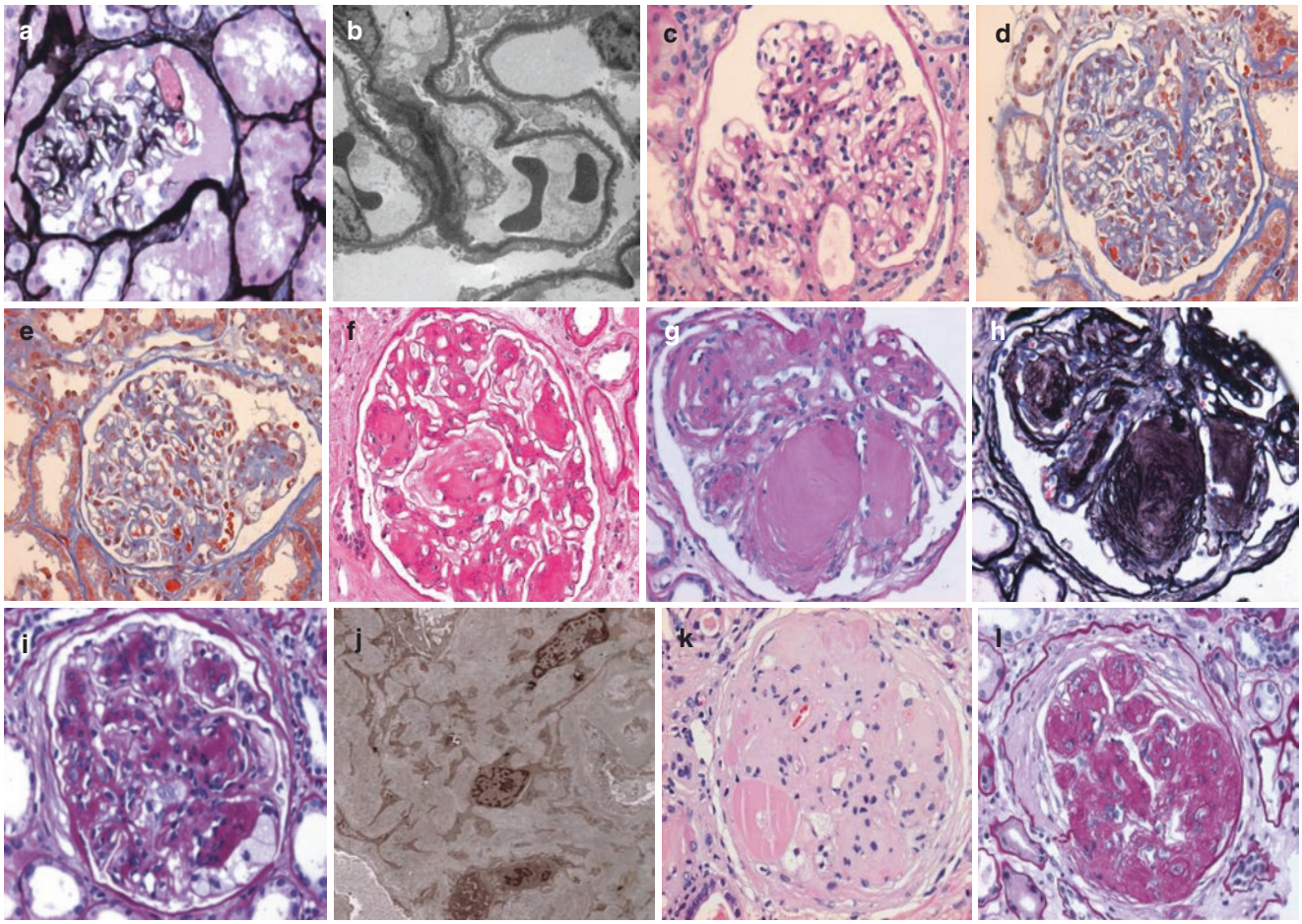

Fig. 55.5 Microphotography showing the different types of diabetic glomerular damage, based on RPS classification. (**a**) Jones Methenamine 40× illustrates a glomeruli with basal membrane irregularities and a microaneurysm. (**b**) Electron microscopy at 2000×, diffuse and homogenous thickening of basal glomerular membrane (RPS Class I). (**c**) PAS 40×, low-moderate expansion of mesangial matrix-generating mesangiosclerosis (Class IIA, RPS). (**d**) Masson's Trichrome 40×, diffuse and homogeneous mesangial thickening, causing glomerular hyperlobulation (Class IIB, RPS). (**e–g**) Microphotography with Masson's Trichrome, PAS [2] and Jones methenamine, respectively. Each at 40×, different stages of acellular collagen forming nodular structures (Class III RPS). (**h**) Residual microaneurysms with endothelial edema within capillary loops, a frequent type of damage in advanced stages of DM. (**i**) Electron microscopy with diffuse collagen deposits within mesangium, characteristic finding in diabetic damage. (**j–l**) H&E and PAS staining, each at 40×, globally sclerosed glomeruli with the presence of hyaline nodules; these findings correspond to DM. When found in most of the glomeruli, it corresponds to Class IV RPS (advanced sclerosis)

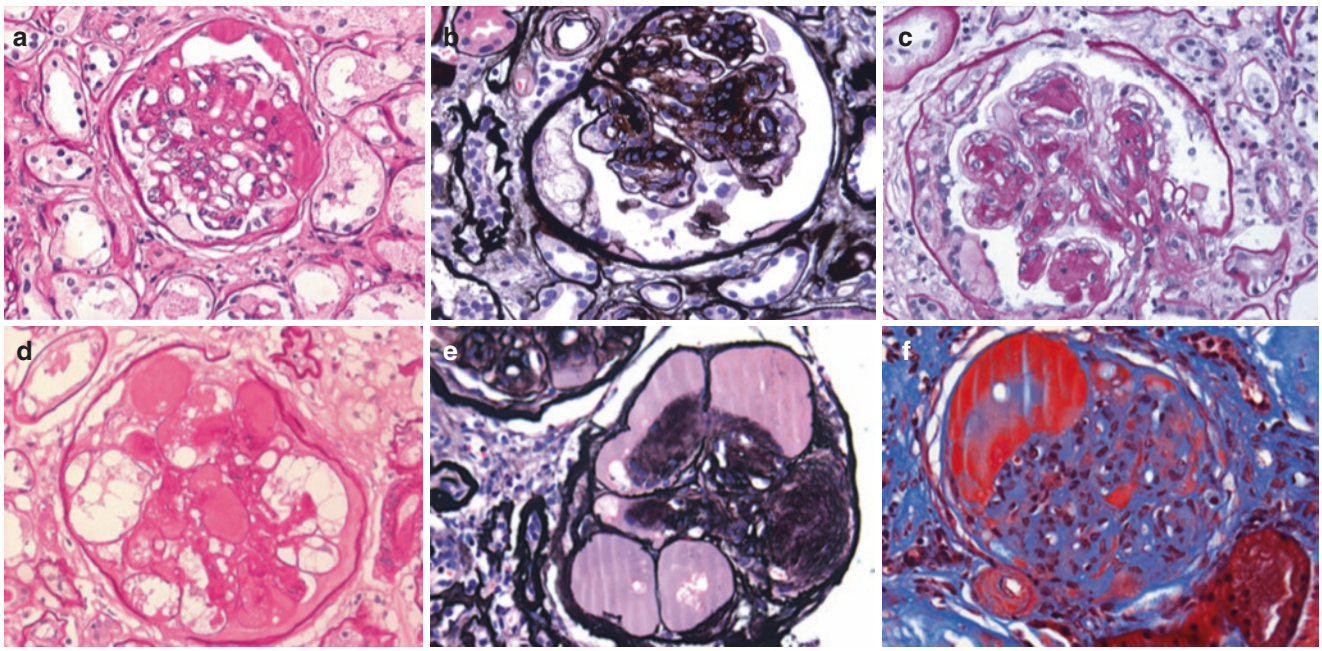

Fig. 55.6 Glomerular insudative lesion. Frequently found in diabetic nephropathy: (**a**) PAS 40×, subcapsular gout, Bowman's capsule-dependent lesion. (**b** and **c**) PAS 40×, fibrous casquet. (**d**–**f**) PAS, Jones methenamine and Masson's Trichrome, respectively. Each at 40× showing glomerular hyalinosis

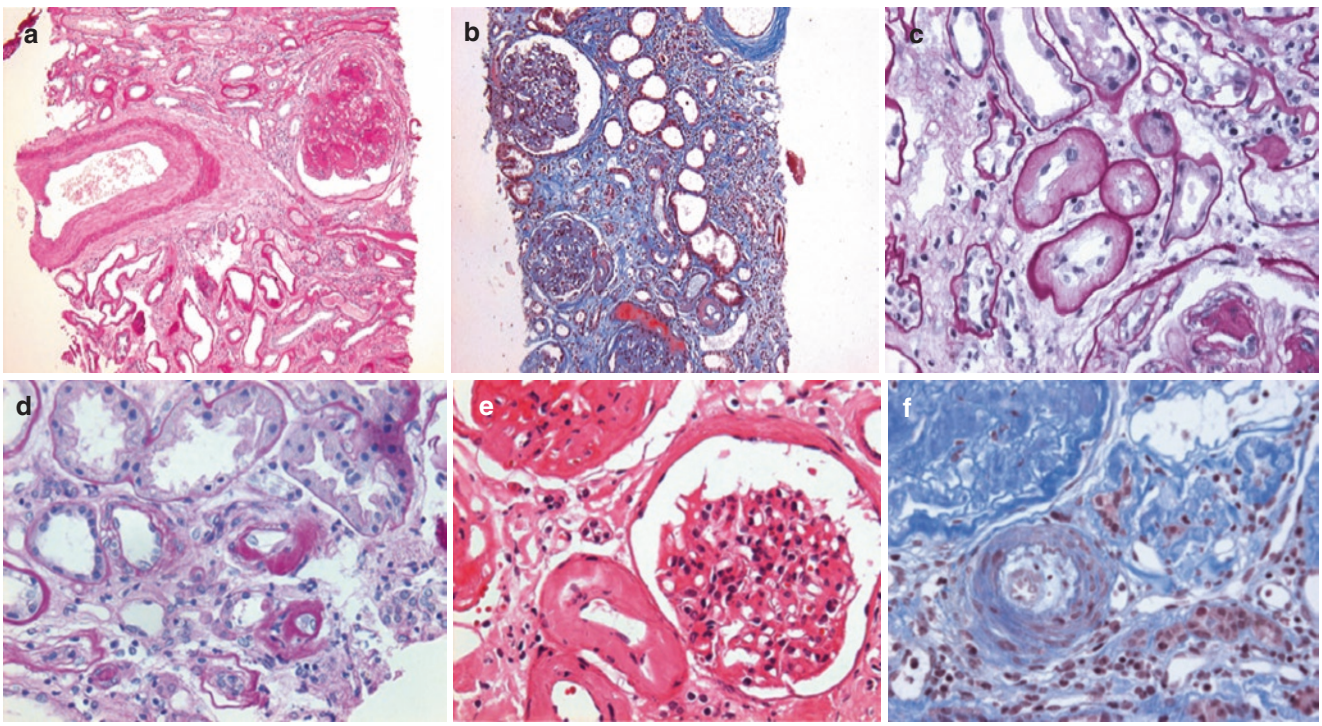

Fig. 55.7 Tubulointerstitial lesions, part of diabetic nephropathy with outmost relevance for renal function prognosis. (**a** and **b**), PAS and Masson's Trichrome 10×, tubulointerstitial fibrosis with loss of tubular "back-to-back" pattern; small caliber arteries present fibrotic damage within arterial intima. (**c**) PAS 40×, lamination and thickening of tubular basal membranes along with atrophic changes. (**d**–**f**) Microvascular lesions in arterioles, PAS, H&E, and Masson's Trichrome, respectively, each at 40×. Advanced arteriolopathy with complete occlusion of vascular lumen. This finding often leads to chronic ischemic glomerular damage and vessel wall hyalinosis, on top of diabetic damage

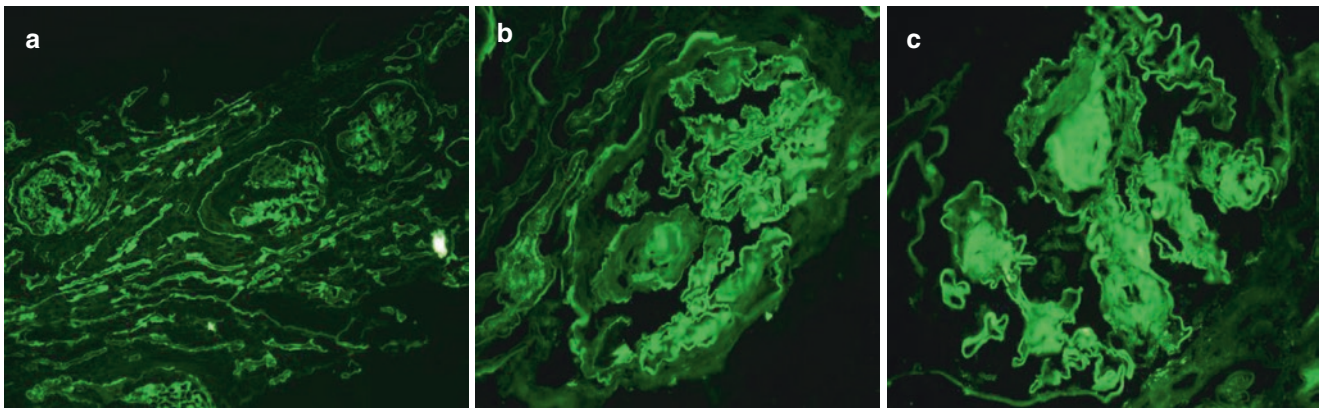

Fig. 55.8 Direct Immunofluorescence in diabetic nephropathy: (**a**–**c**) Albumin 10× and 40× and IgG 40×, respectively. Hyperfiltration generates linear positivity in glomerular and tubular basal membranes. Albumin shows tubular cytoplasmic reabsorption vacuoles

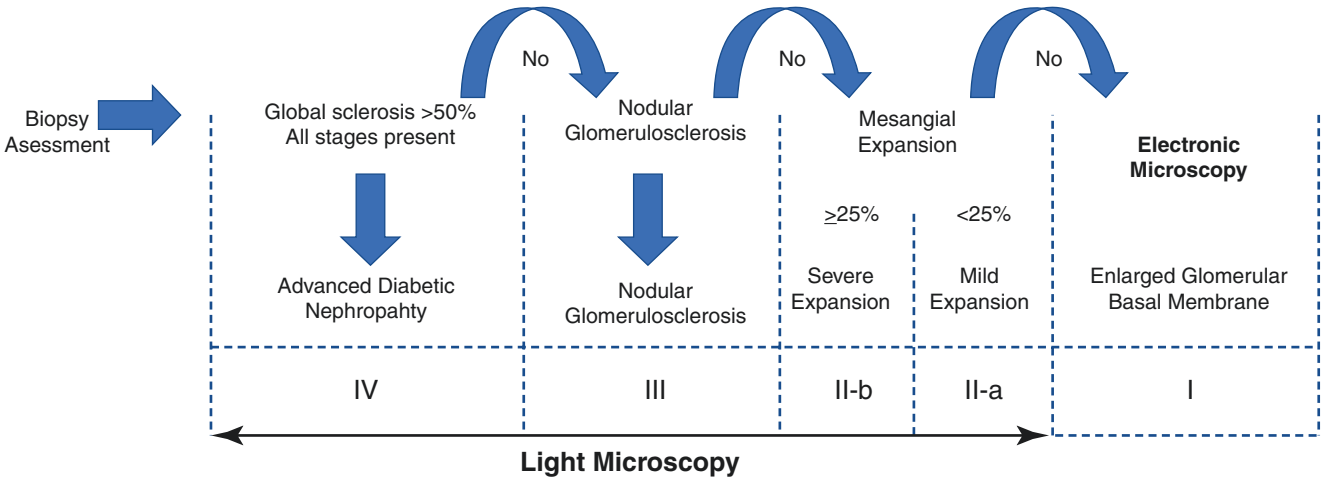

Fig. 55.9 Proposed assessment of kidney biopsy in diabetic nephropathy. (Adapted and modified from as described by Tervaert TWC, Mooyaart AL, Amann K, Cohen AH, Cook HT, and Drachenberg CB et al. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol. 2010;21 (4):556–63)

Tissue out of paraffin block can also be used for indirect immunoperoxidase technique, although with the paramount disadvantage of a less sensitive study.

Diabetic kidney disease continuum implies that histopathologic lesions will not be all at the same stage. A collage of microscopic lesions, from incipient to advanced, will be found. Prevailing histologic findings and the clinical picture ultimately lead to classification, considering an orderly mannered approach by glomerular, interstitial, and vascular findings. It should be emphasized that, being diabetes mellitus such a common entity, it is not uncommon to describe diabetic nephropathy on top of many other nondiabetic entities.

Advanced IFTA is considered the histologic manifestation of end-stage renal disease. As to vessel histology, even though the Renal Pathology Society classification does not make distinction between afferent and efferent arteriolar hyalinosis, it is considered that efferent arteriolar hyalinosis is the most specific vessel finding for diabetic nephropathy, since involvement of the afferent arteriole (afferent arterial hyalinosis) might be present in other entities.

We proposed a flowchart for the evaluation of DKD in kidney biopsy (Fig. 55.9).

It is important to stand out that KDIGO (Kidney Disease: Improving Global Outcomes) 2021 guidelines have proposed the distinction between diabetic nephropathies in which, based on histology, we can affirm such diagnosis. All other cases in which diabetes, albuminuria/proteinuria, and/or diminish glomerular filtration rate are present but without histologic tissue to claim diabetic nephropathy, should be named as diabetic kidney disease (DKD) [43].

Prevention of Diabetic Nephropathy

Avoiding the development of diabetic nephropathy involves treatment of diabetes per se. Glycemic control, antihypertension therapy, and dyslipidemia management are common and comorbid entities that directly impact on the evolution to diabetic nephropathy. However, this is beyond the scope of this chapter, and we will focus specifically on DKD management.

Treatment of Diabetic Nephropathy

Non-pharmacologic Intervention

Salt Intake

Salt intake is associated with increased blood pressure, and therefore, it is considered a risk factor for uncontrolled hypertension and end organ damage with DKD progression. In a systematic review and meta-analysis, by pooling studies with salt reduction in type 1 and type 2 diabetic patients, 13 trials and 254 individuals were included. Mean duration of salt restriction was 1 week for both types of diabetic patients, and median reduction of urinary sodium was 11.9 g/day for type 1 diabetic patients and 7.3 g/day for type 2 diabetic patients. Blood pressure was reduced by −7.11 systolic and −3.13 diastolic mmHg in individuals with type 1 diabetes and −6.90 systolic and −2.87 diastolic mmHg in individuals with type 2 diabetes. The impact of this intervention was considered as effective as the use of one antihypertension medication, and as such, it should be applied to all diabetic patients [44].

Besides salt restriction effect on hypertension, renal and cardiovascular benefits have been described for reduced salt intake in addition to RAAS blockade. The former was described in a pooled analysis of type 2 diabetic patients of RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) and IDNT (Irbesartan Diabetic Nephropathy Trial) trials. The former analysis included 1177 participants with established DKD assigned to angiotensin receptor blocker therapy, losartan for RENAAL or irbesartan for IDNT populations, or non-RAAS inhibitors (non-RAASi), further stratified according to urine sodium/creatinine ratio into tertiles of <121 mmol/g (<2.78 g of sodium, <6.05 g of salt), 121–153 mmol/g (2.78–3.51 g of sodium, 6.05–7.65 g of salt), and equal or ≥153 mmol/g. Renal outcomes were defined as a composite of doubling serum creatinine from baseline, serum creatinine ≥6.0 mg/dL, and need for chronic dialysis or transplantation. Cardiovascular outcomes were defined as a composite of death, myocardial infarction, stroke, hospitalization for heart failure, or revascularization procedures. Within ARB and RAASi groups, renal outcomes for ARB therapy in the lower tertile of sodium/creatinine urine ratio had a HR 0.57 (95% CI 0.39–0.84) vs. non RAASi in higher tertile with HR 1.37 (95% CI 0.96–1.96), $P < 0.001$. Same groups for cardiovascular outcomes reported HR 0.65 (95% CI 0.43–0.92) versus HR 1.25 (95% CI 0.89–1.75), $P = 0.021$. Significant difference for renal and cardiovascular endpoints disappeared between groups when comparing high urine sodium/creatinine ratio tertiles [45].

The former illustrates sodium restriction which enhances the renal and cardiovascular benefits of angiotensin receptor antagonism on type 2 diabetic population with DKD.

Protein Restriction

Protein overload hastens renal decline by different mechanisms. Pancreas responds to protein ingestion by increasing glucagon secretion; glucagon generates afferent arteriole vasodilation and increases systemic hemodynamics over the glomerulus. Along with the former, filtrated amino acids are reabsorbed by the proximal convoluted tube with sodium and chloride, which reduces the chloride available to the juxtaglomerular apparatus. The latter leads to the absence of tubuloglomerular feedback, further increasing afferent arteriole dilation. Finally, protein overload to the renal parenchyma, in a low renal mass stage, increases profibrotic cytokines, such as transforming growth factor beta-1 and platelet-derived growth factor [46].

Due to the former mentioned mechanisms of action, low protein diet (LPD, 0.6–0.8 g/kg of body weight/day) was proposed as a therapeutic intervention and proved to be effective in animal models along with nondiabetic kidney disease clinical trials [47]. Therefore, recommendation of LPD was extended to DKD by KDIGO (Kidney Disease Improving Global Outcomes) guidelines [47]. Nonetheless, in diabetic kidney disease, evidence is less clear; there are clinical trials and pooled meta-analysis both pro and against LPD as an effective intervention to slow kidney function decline [46, 47]. A definitive evidence-based recommendation cannot be established.

Interesting proposals are being considered such as starting LPD in eGFR higher than 30 mL/min/1.73 m^2 to preserve eGFR in earlier stages and to avoid malnourishment frequently seen in advanced CKD due to protein energy wasting. In addition, it has been proposed that maintaining or increasing caloric intake and switching carbohydrate, protein, and fat proportions could be of further benefit [46–49].

Pharmacologic Interventions

Renin-Angiotensin-Aldosterone System (RAS)

There is a large body of evidence to back up the use of RAS blockade in DKD being the cornerstone of DKD therapy. ACE inhibitors and ARBs have earned this position due to

their positive effect on glomerular filtration preservation, reduction in the development, and progression of proteinuria along with lowering interstitial fibrosis. ACE inhibitors and ARBs are used indistinctly as their effect on the RAS system is directed toward decreasing its activation, even though most of the available evidence for ACE inhibitors is related to type 1 diabetes and for ARBs to type 2 diabetes.

Physiologic explanation of their benefit comes from their effect in systemic and glomerular hemodynamics, by decreasing not only systemic blood pressure but also by decreasing vasoconstriction on efferent arteriole and reducing direct pressure over the glomerulus. The former effect reduces the hyperfiltration phenomenon and clinically translates into GFR preservation and avoidance of proteinuria development, progression, or even regression.

The former was demonstrated in type 1 diabetics in the Collaborative Study Group, where 207 patients received captopril 25 mg three times a day and 202 patients placebo, to a blood pressure goal of ≤140/90 mmHg with a 3-year follow-up. Inclusion criteria corresponded to proteinuria (defined as ≥500 mg per day) and serum creatinine (SCr) of ≤2.5 mg/dL; the primary outcome was doubling of the serum creatinine. By the end of the study, 25 patients in the captopril group and 43 patients in the placebo group had reached the primary outcome, with 48% risk reduction for the captopril group. Subgroup analysis demonstrated that the effect of captopril on outcomes was higher in individuals with increased serum creatinine concentration, 76% for mean SCr 2.0 mg/dL, 55% for mean SCr 1.5 mg/dL, and 17% for 1.0 mg/dL. From the eGFR standpoint, decline in creatinine clearance was 11+/− 21% in captopril group and 17+/−20% in the placebo group ($p = 0.03$) [50].

As for anti-proteinuric effect, a systematic review and meta-analysis that included 646 type 1 diabetic patients (10 clinical trials) with normotensive and moderate increased albuminuria DKD evaluated ACE inhibitor therapy against placebo for this outcome. Reduction in progression to severe albuminuria was reported with an odds ratio of 0.38 (95% CI 0.25–0.57) and regression to low-level albuminuria by 3.07 (95% CI 2.15–4.44). Follow-up at 2 years found 50.5% lower albuminuria in ACE inhibitor-treated patients, compared to placebo ($p < 0.001$) with effect none entirely explained by blood pressure control [51].

In type 2 diabetes, effect of RAS blockade by ARBs also demonstrated reduction in the development and progression of proteinuria along with reduction in GFR decline. The preventing microalbuminuria in type 2 diabetes study (BENEDICT [Bergamo Nephrologic Diabetes Complications Trial]) assessed onset and development of moderately increased albuminuria (primary endpoint) in normoalbuminuric, hypertensive, type 2 diabetic patients. The intervention consisted of a combination of ACEI (trandolapril) and calcium channel blocker (verapamil), either ACEI or calcium channel blocker alone or placebo. Target blood pressure for all participants was 120/80 mmHg, and other antihypertensive medications were allowed to goal. The trial recruited 1204 participants, with a median follow-up of 3.6 years; primary outcome (moderately increased albuminuria) was reached by 5.7% of participants in the combined treatment group, 6.0% in only ACEI group, 11.9% of those receiving calcium channel blocker alone, and in 10% of participant in the placebo group.

In established DKD, a multicentric, randomized, double-blinded, placebo-controlled trial with irbesartan recruited 590 patients with type 2 diabetes and moderately increased albuminuria, assigned groups to placebo, irbesartan 150 mg/day or irbesartan 300 mg/day, with a 2-year follow-up for a primary outcome of severely increased albuminuria or at least 30% increase from baseline. In the intervention arms, 5.2% of patients (10/194) for the 300 mg irbesartan group and 9.7% of patients (9/195) for the 150 mg irbesartan group reached primary outcome, as compared to 14.9% of patients (30/201) in the placebo arm resulting in 70% reduction in albuminuria progression for intervention groups [52]. Regarding GFR, the RENAAL study gathered 1513 patients with type 2 diabetes and randomized to losartan 50 mg, 100 mg, or placebo on top of conventional antihypertensive medication, for a 3.4-year follow-up. Primary outcome was a composite of doubling serum creatinine, and development of end-stage renal disease or death. Secondary outcomes were a composite of morbidity and mortality from cardiovascular causes, proteinuria, and the rate of progression of renal disease. Primary composite was reduced by 16%, double of serum creatinine by 25%, development of end-stage renal disease by 28%, and proteinuria declined by 35% in the losartan groups. There was no effect on mortality [53].

Given the former mentioned data, and many other studies sustaining similar results, double blockade with ACE inhibitor and ARB was explored to obtain more effective results on renal outcomes. The ONTARGET (Ongoing Telmisartan Alone in Combination with Ramipril Global Endpoint Trial) study disregarded the benefit of combined therapy. Such treatment proved increased adverse effects as a composite of need for acute dialysis, double of serum creatinine, and death. The first two endpoints of the composite sustained in individual analysis [54].

Another study to assess the benefit from double blockade in DKD was the Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy (VA Nephron-D), which assigned standard baseline therapy of losartan 100 mg per day and randomized participants to lisinopril 10–40 mg per day or placebo. Primary endpoint was eGFR decline, ESRD, and death; secondary endpoint was defined as first occurrence of eGFR decline or ESRD, and safety outcomes were mortality,

hyperkalemia, and acute kidney injury. A total of 1448 type 2 diabetic patients with severely increased albuminuria and an eGFR within 30 and 89.9 mL/min/1.73 m^2 were included and followed for median of 2.2 years. The study was stopped early for significant increased adverse effects in double RAS inhibition groups: hyperkalemia (6.3 events/100 person-years vs. 2.6 events/100 person-years, $p < 0.001$) and acute kidney injury (12.2 vs. 6.7 events/100 person-years, $P < 0.001$) [55].

Aldosterone antagonism has become a valuable tool in the management of chronic kidney disease, for up to 53% of patients on conventional RAS blockade will develop aldosterone escape phenomenon by the end of a 1-year therapy [56]. Compared to ACE inhibitors or ARBs alone, nonselective aldosterone blockade (spironolactone) on top of ACE inhibitors or ARBs significantly reduced 24 h proteinuria [57]. Narrowing to DKD, systematic review and meta-analysis of 7 trials (287 patients) compared ACEI or ARB versus combination therapy of MRA (spironolactone or eplerenone) plus ACEI or ARB. Results showed significantly reduced albuminuria excretion by 69.38% (95% CI -103.53 to −35.22, $p < 0.0001$). As for blood pressure, comparing 296 patients with combined MRA RAS blockade therapy versus 281 patients with RAS blockade alone, significantly decreased systolic and diastolic values were reported, with mean difference − 5.61 (95% CI -9.38 to −1.84, $p = 0.004$) for systolic and − 2.17 (95% CI -4.23 to −0.11, $p = 0.04$) for diastolic blood pressure [57]. In 11 trials pooling within this meta-analysis, GFR did not improve, and as expected, hyperkalemia developed much more (16 studies, 1684 patients) with relative risk of 3.74 (95% CI 2.30–6.09, $p < 00001$) [56].

Summarizing the former evidence, RAS blockade, for which ACEI and ARB have been used interchangeably, is the cornerstone therapy for diabetic kidney disease both in type 1 and 2 diabetes. RAS blocking therapy impacts on the reduction of albuminuria, preservation of GFR, and lowering of fibrotic remodeling. MRA with spironolactone on top of RAS blockade compensates for aldosterone breakthrough, and its major effect is reflected over proteinuria and blood pressure control.

Novel Therapies

Sodium Glucose Transporters

Hyperglycemia induces the proximal convoluted tubule to increase glucose claim, the former is performed in company of sodium, by means of sodium-glucose transporters 1 and 2 (SGLT-1 and SGLT-2, respectively). This leads to a lesser available sodium to be sensed downstream by the macula densa, and as a result, afferent glomerular arteriole is dilated, exposing the glomerulus to direct blood pressure damage while enhancing hyperfiltration phenomenon. Inhibition of sodium-glucose transporters leads to glucosuria and downstream sodium overflow, allowing actual caloric/glucose loss as a desired effect for diabetes treatment in addition to activation of tubule-glomerular feedback.

If we combine RAS blockade with SGLT-2 therapy, we obtain the exact opposite glomerular hemodynamics of diabetic kidney disease pathophysiology. The renal hemodynamics go from dilated afferent and narrowed efferent arterioles, with increased exposure to systemic blood pressure and hyperfiltration on the glomerulus, to a narrow afferent and dilated efferent arteriole, with the opposite effect.

The benefit from the former hypothesis has been tested with positive results in different cardiovascular and renal outcome studies for iSGLT-2. In EMPA-REG OUTCOME trial, type 2 diabetic patients with established cardiovascular disease and eGFR equal or greater than 30 mL/min/1.73 m^2 of BSA were randomly assigned to receive placebo, empagliflozin 10 mg/day, or 25 mg/day for a median duration of treatment of 2.6 years and median observation time of 3.1 years. RAS blockade, by means of ACEI or ARB, was present in 80.7% of study population at baseline. As for renal outcomes, incident or worsening nephropathy (progression to severely increased albuminuria) occurred in 12.7% in empagliflozin groups versus 18.8% in the placebo group, 0.61 (95% CI 0.53–0.70, $P = <0.001$). Doubling of serum creatinine with a decrease of eGFR to ≤45 mL/min/1.73 m^2 BSA was 1.5% versus 2.6% in empagliflozin and placebo, respectively, with a relative risk reduction of 44%. Renal replacement therapy was initiated in 13 of 4687 patients in empagliflozin and 14 of 2333 patients in the placebo group, with a relative risk reduction of 55%. Regarding incident albuminuria, there was no difference between medication and placebo groups. The composite of incident or worsening nephropathy or cardiovascular death had a HR for empagliflozin of 0.61 (95% CI 0.55–0.69, $p < 0.001$) [58].

Estimated GFR lowered during the first 4-week period trial in the empagliflozin arms to a mean of −0.82 ± 0.04 mL/min/1.73 m^2 of BSA for the 25 mg/day and was less evident for the 10 mg/day dose. Estimated GFR remained stable after such period, and mean eGFR annual decline for intervention groups was 0.19 ± 0.11 mL/min/1.73 m^2 BSA compared to 1.67 ± 0.13 mL/min/1.73 m^2 BSA in the placebo group, $p < 0.001$. After cessation of trial medication, empagliflozin groups increased eGFR up to 0.55 ± 0.04 mL/min/1.73 m^2 BSA, making evident the hemodynamic effect of the medication [58].

The Canagliflozin and Cardiovascular Events in Type 2 Diabetes (the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program), another trial for SGLT-2 inhibition, included two sister trials, the CANVAS and CANVAS-R. Both studies were multicentric, double-blinded, randomized, and placebo-controlled. 10,142 DKD participants were assigned to canagliflozin 300 mg/day, 100 mg/day, or placebo for CANVAS and canagliflozin

100 mg/day (with option to increase up to 300 mg/day) or placebo for CANVAS-R. Primary outcome was a composite of death from cardiovascular cause, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes were death from any cause, death from cardiovascular cause, progression of albuminuria (30% increase from baseline and category upgrade between normoalbuminuria and moderately or severely increased albuminuria), and another composite of death from cardiovascular cause and hospitalization for heart failure. The mean follow-up was 188.2 weeks. Canagliflozin group had statistically significant less composite of death from cardiovascular cause, nonfatal myocardial infarction, and nonfatal stroke, 26.9 participants per 1000 patient-years versus 31.5 for placebo (HR 0.86, 95% CI 0.75–0.97, $P < 0.001$ non-inferiority and $p = 0.02$ for superiority). Regarding renal outcomes, albuminuria progression was less frequent in intervention groups, 89.4 events per 1000 patient-years versus 128.7 for placebo (HR 0.73, 95% CI 0.67–0.79), along with regression of albuminuria, with 293.4 patients per 1000 patient-years for intervention groups versus 187.5 for placebo (HR 1.70, 95% CI 1.51–1.91). Renal composite of sustained 40% reduction in eGFR, the need for renal replacement therapy, or death from renal causes occurred less in intervention groups, 5.5 in canagliflozin versus 9.0 in placebo per 1000 patient-years (HR 0.60, 95% CI, 0.47–0.77). Death from any cause was not different between canagliflozin and placebo groups [59].

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes (DECLARE-TIMI 58) study randomized patients with type 2 diabetes who have or were at risk for atherosclerotic cardiovascular disease to dapagliflozin or placebo for primary outcomes of major adverse cardiovascular events (MACE) of cardiovascular death, myocardial infarction, or ischemic stroke, and secondary outcomes of renal composite composed of ≥40% decrease in eGFR to less than 60 mL/min/1.73 m^2 of BSA, new end-stage renal disease, death from renal or cardiovascular causes, and death of any cause. A total of 17,160 patients were evaluated, most of which did not have atherosclerotic cardiovascular disease, a primary prevention group of 10,186 patients. Patients were followed for a median of 4.2 years; dapagliflozin was non-inferior to placebo in MACE but did not achieve superiority. Only benefit in a composite of cardiovascular death or hospitalization for heart failure was found, with a 17% relative risk reduction at the expense of lower heart failure events, for there was no difference in cardiovascular events within groups [60].

CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation). The goal of the trial was to assess the effect of canagliflozin on renal outcomes among patients with type 2 diabetes mellitus (DM2) and chronic kidney disease (CKD). Patients were randomized in a 1:1 fashion to either canagliflozin 100 mg daily ($n = 2202$) or matching placebo ($n = 2199$). Four thousand four-hundred patients were included with a mean follow-up of 2.62 years. The trial stopped early due to overwhelming benefit. The primary outcome of end-stage renal disease (ESRD), doubling of serum creatinine, and renal or cardiovascular (CV) death, for canagliflozin versus placebo, was 43.2 versus 61.2 per 1000 patient-years (P-Y) ($p = 0.00001$): doubling of serum creatinine, 20.7 versus 33.8/1000 P-Y ($p < 0.001$) for canagliflozin versus placebo, and ESRD, 20.4 versus 29.4/1000 P-Y ($p = 0.002$) for canagliflozin versus placebo [61].

DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease). The DAPA-CKD trial was a multinational, multicenter, event-driven, randomized, double-blind, parallel-group, placebo-controlled study involving 4304 patients with CKD and eGFR ≥25 mL/min/1.73 m^2, but ≤75 mL/min/1.73 m^2, and a UACR ≥200 mg/g, but ≤5000 mg/g, with or without type 2 diabetes (T2D). As occurred in the CREDENCE trial, the trial was stopped early due to overwhelming efficacy. Over a median of 2.4 years, a primary outcome event occurred in 197 of 2152 participants (9.2%) in the dapagliflozin group and 312 of 2152 participants (14.5%) in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.51–0.72; $P < 0.001$). The hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45–0.68; $P < 0.001$), and the hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55–0.92; $P = 0.009$). For the first time, this trial demonstrated similar efficacy in subjects with and without diabetes [62].

EMPA-KIDNEY (Empagliflozin in Patients with Chronic Kidney Disease) is an ongoing trial to evaluate renal and cardiovascular outcomes in 6600 patients for the use of empagliflozin on CKD profession; different to other trials, EMPA-KIDNEY would include lower eGFR (CKD-EPI eGFR ≥20–<45 mL/min/1.73 m^2 or) and CKD-EPI eGFR ≥45–<90 mL/min/1.73 m^2 and lower urinary albumin/creatinine ratio ≥ 200 mg/g (or protein/creatinine ratio ≥ 300 mg/g) (Clinical Trial NCT03594110).

Considerations as to adverse effects of SGLT-2 inhibitors as a group include an increased risk for euglycemic ketoacidosis, perineum-necrotizing fasciitis, genitourinary tract infections, hypotension, and acute kidney injury. Medication-specific adverse effects have been described, as in canagliflozin-treated patients, increased incidence for bone fracture, and mid foot/toe amputations. Amputations occur more often in patients with lower-extremity peripheral artery disease and/or diabetic foot.

GLP1 Receptor Agonists (GLP1AR)

Cardiovascular outcome trials for GLP1AR in diabetic population have included chronic kidney disease patients. Data from these trials proved a favorable profile for lixisenatide, exenatide, liraglutide, semaglutide, albiglutide, and dulaglutide for decreasing in albuminuria and may have an effect in lowering eGFR decline rate. Meta-analysis of seven GLP1AR cardiovascular risk outcome trials pooled a 17% risk reduction compared to placebo for a renal composite of severely increased albuminuria, eGFR decline, progression to kidney failure, or death from kidney disease.

As for today, there has not been a completed GLP1RA kidney outcome trial. The Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects with Type 2 Diabetes and Chronic Kidney Disease (FLOW) trial started on 2019 and is expected to be completed by 2024 [63].

Finerenone

As previously mentioned, MRAs proved reduction in albuminuria for diabetic and nondiabetic CKD. Finerenone (FRN) is a more selective MRA than spironolactone, with more affinity than eplerenone. Finerenone was evaluated for DKD in the ARTS-DN study, a multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 2B trial in which finerenone at different doses (1.25 mg/day, 2.5 mg/day, 5 mg/day, 7.5 mg/day, 10 mg/day, 15 mg/day, 25 mg/day) or placebo was administered to patients with DKD already on RAS blockade. Eligibility criteria were type 2 diabetic patients already on RAS blockade, with at least moderately increased albuminuria, eGFR ≥30 mL/min/1.73 m^2, first visit serum potassium concentration ≤ 4.8 mmol/L, and 4-week or longer stable non-potassium-sparing diuretic use. Endpoints were evaluation of albuminuria reduction at the end of the 90-day period and adverse effects such as hyperkalemia and eGFR reduction. Effect on albuminuria excretion rate (AER) was noticed in an increasing dose-dependent effect starting on finerenone 7.5 mg/day. Placebo-corrected mean ratios of AER, according to dose, were FRN 7.5 mg/day, 0.79 (90% CI 0.68–0.91, $p = 0.004$), FRN 10 mg/day, 0.76 (90% CI 0.65–0.88, $p = 0.001$), FRN 15 mg/day 0.67 (90% CI 0.58–0.77, $p < 0.001$), and FRN 20 mg/day 0.62 (90% CI 0.54–0.72, $p < 0.001$). Hyperkalemia was reported for the 7.5-, 15-, and 20 mg/day groups in 2.1%, 3.2%, and 1.7%, respectively. There was no difference in eGFR decrease rate of ≥30% [64].

This study suggests the potential benefit from finerenone as another MRA with a lesser adverse effect and dose-dependent effect on reducing albuminuria. Nonetheless, it must be noticed that on the trial, 60% of patients had eGFR of 60 mL/min/1.73 m^2 or more, and serum potassium higher than 4.8 mmol/L was considered an exclusion criteria. Hard endpoints such as cardiovascular events, progression to end-stage renal disease, and dialysis requirement are currently being explored; most recent studies in this regard are FIGARO (Facilitated Immunoglobulin Administration Registry and Outcomes Study) and FIDELIO (Finerenone in Reducing Kidney Failure and Disease Progression).

FIGARO was a double-blind, randomized study that explored cardiovascular outcomes for CKD population with type 2 diabetes treated with finerenone. Eligibility criteria required patients to have ACR of 30 to less than 300 mg/g, eGFR of 25–<90 mL/min per 1.73 m^2 (stage 2–4 CKD) or ACR of 30 to less than 5000 mg/g, and eGFR >60 mL/min per 1.73 m^2 (stage 1 or 2 CKD), both groups on top of maximum tolerated RAAS blockade. Primary outcome was time to event composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. Secondary outcome was kidney failure, sustained decrease of ≥40% in eGFR from baseline, or death from renal causes. Randomization was 7437 patients to finerenone of placebo. Finerenone achieved during a 3.4-year median follow-up, 13% relative risk reduction in primary composite (HR 0.87; 95% CI 0.76–0.98, $P = 0.03$), and 13% relative risk reduction for secondary composite (HR 0.87; 95% CI 0.76–1.01) [65].

FIDELIO was a kidney outcome-driven study for finerenone in chronic kidney disease with type 2 diabetic patients. It was a randomized, double-blind, placebo-controlled trial with 1:1 assignment of 5734 patients to finerenone or placebo. Inclusion criteria were a composite of albumin to creatinine ratio (ACR) of 30 to less than 300 mg/g, eGFR of 25–<60 mL/min per 1.73 m^2 and diabetic retinopathy, or ACR of 300–500 mg/g and eGFR of 25–<75 mL/min per 1.73 m^2. All patients are on maximum tolerated dose of RAAS blockade. The primary outcome was a time-to-event composite of kidney failure, sustained decrease of ≥40% in eGFR from baseline, or death from renal causes. Secondary outcomes were death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure. Results for finerenone after a 2.6-year of follow-up were a primary outcome relative risk reduction of 18% (HR 0.82, 95% CI 0.73–0.93; $P = 0.001$) and a secondary outcome relative risk reduction of 14% (HR 0.86, 95% CI 0.75–0.99, $P = 0.03$), lowering risks of progression for CKD and cardiovascular events compared to placebo [66].

Conclusions

Diabetic kidney disease remains the main cause of end-stage kidney failure in the world. Although mechanisms of disease are now better understood, the only accepted medical treat-

ment for DKD is RAS inhibition. Despite this treatment, many patients still progress to kidney failure. Double RAS inhibition is no longer recommended based on two randomized trials. Newer agents such as SGLT-2 inhibitors, GLP1 receptor antagonists, and finerenone are novel and promising therapies that have modified the natural history of the disease. There is still lack of sufficient evidence to combine these agents; however, it is possible that targeting different pathways will result in improved outcomes.

Multiple Choice Questions

1. Which of the following structures must become damaged in order to develop albuminuria:
   (a) Distal collecting duct
   (b) **Glicocalix**
   (c) Juxtaglomerular apparatus
   (d) Urea counter current mechanism
2. The following pathways are responsible for the hyperfiltration mechanism:
   (a) Hexosamine pathway
   (b) Metabolic pathway
   (c) **Hemodynamic pathway**
   (d) Autophagy
3. Hyperfiltration develops in diabetic nephropathy by effect of which of the following:
   (a) Afferent arteriole vasoconstriction
   (b) **Efferent arteriole vasoconstriction**
   (c) Juxtaglomerular apparatus dysfunction
   (d) Glomerular basal membrane thickening
4. Nephropathology description of diabetic nephropathy is based on:
   (a) Electron microscopy description
   (b) Immunofluorescence description
   (c) **Light microscopy description**
   (d) Kimmelstiel-Wilson nodules
5. Earliest nephropathologic findings in diabetic nephropathy.
   (a) Mesangial expansion
   (b) Tubular atrophy
   (c) Interstitial fibrosis
   (d) **Glomerular basal membrane thickening**
6. Most effective treatment for established diabetic nephropathy is based on:
   (a) Endothelin receptor blockade
   (b) Protein restriction
   (c) Diuretic use
   (d) **Renin-angiotensin-aldosterone system blockade**
7. SGLT-2 inhibitor treatment produces which of the following hemodynamic effects in the glomerulus:
   (a) **Vasoconstriction of afferent arteriole**
   (b) Vasodilation of afferent arteriole
   (c) Vasodilation of efferent arteriole
   (d) Vasoconstriction of efferent arteriole
8. Mineralocorticoid antagonist therapy should be considered to compensate for which of the following:
   (a) Hyperfiltration phenomenon
   (b) Albuminuria
   (c) **Aldosterone breakthrough**
   (d) Diuretics hypokalemia effect
9. Overt diabetic nephropathy without treatment leads to glomerular filtration rate loss of.
   (a) **1 mL/min month**
   (b) 1 mL/min week
   (c) 1 mL/min year
   (d) 50% of baseline within first 6 months
10. Which of the following findings must be considered to perform kidney biopsy in diabetic patients
    (a) Development of albuminuria within the first 5 years of diabetes diagnosis
    (b) Development of albuminuria in absence of diabetic retinopathy
    (c) Development of nephrotic syndrome
    (d) **All the above**

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Peripheral Diabetic Neuropathies

56

Gergely Feher

Introduction

More than 25% of the US population aged ≥65 years has diabetes, and the aging of the overall population is a significant driver of the diabetes epidemic. The epidemic is chiefly of type 2 diabetes and also the associated conditions known as 'diabesity' and 'metabolic syndrome'. In conjunction with genetic susceptibility, particularly in certain ethnic groups, type 2 diabetes is brought on by environmental and behavioural factors such as a sedentary lifestyle, overly rich nutrition and obesity. The prevention of diabetes and control of its micro- and macrovascular complications will require an integrated, international approach if we are to see significant reduction in the huge premature morbidity and mortality it causes [1]. Diabetic neuropathies (DN) encompass a wide range of nerve abnormalities and are common, with prevalence rates reported between 5% and 100% depending on the diagnostic criteria. Diabetic peripheral neuropathy (DPN) is associated with considerable morbidity, increased mortality and diminished quality of life, causing a tremendous economic burden [2]. The duration and severity of hyperglycaemia, presence of dyslipidemia, hypertension and smoking are major risk factors for the development of diabetic polyneuropathy [3]. The different mechanisms involved in different pain sensations are still poorly understood, but there is ample evidence that abnormal discharges from diseased somatosensory neurons are responsible. Spontaneous activity in the peripheral nociceptor system may also trigger central nervous system changes responsible for hyperalgesia and allodynia [1].

Epidemiology

Diabetic peripheral neuropathy (DPN) is a common complication of both type 1 and type 2 diabetes. Despite the different pathophysiologies, there has been a longstanding assumption that the mechanism leading to DPN is shared. Type 2 DM is much more common (90–95%) but has a slightly lower lifetime incidence of neuropathy; the reported prevalence varies between 6 and 51% compared with the 54–59% associated with type 1 DM [4, 5]. The primary risk factor for DPN is hyperglycaemia, but apart from chronic hyperglycaemia, recent studies showed the possible role of large or frequent serum glucose level fluctuations as a possible trigger factor [5]. Whereas treating hyperglycaemia in type 1 DM can significantly reduce the incidence of neuropathy by up to 60–70%, glucose control in type 2 DM has only a marginal 5–7% reduction in the development of neuropathy estimated to affect 30–50% of individuals with diabetes. Many recent studies have implicated cardiovascular risk factors which include age, duration of disease, cigarette smoking, hypertension, elevated triglycerides, higher BMI, alcohol consumption and taller height in the background of DN [1, 4]. Interestingly, between 25% and 62% of patients with idiopathic peripheral neuropathy are reported to have prediabetes, and among individuals with prediabetes, 11–25% are thought to have peripheral neuropathy, and 13–21% have neuropathic pain. Population-based studies suggest a gradient for the prevalence of neuropathy, being highest in patients with manifest diabetes mellitus, followed by individuals with impaired glucose tolerance and then impaired fasting glucose and least in those with normoglycaemia [4].

Pathophysiology

It is generally believed that oxidative stress is the key pathological process inducing nerve damage in diabetes. Oxidative stress, possibly triggered by vascular abnormalities and asso-

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ciated microangiopathy in the nerve, is a key pathological process inducing nerve damage in diabetes in humans and experimental models. Diabetes-induced oxidative stress in animal models of in type 1, type 2 and pre-diabetes in sensory neurons and peripheral nerve is demonstrated by increased production of reactive oxygen species (ROS), lipid peroxidation and protein nitrosylation and diminished levels of reduced glutathione and ascorbate. Treatment with antioxidants such as α-lipoic acid, γ-linolenic acid and aldose reductase inhibitors prevents many indices of neuropathy in STZ (streptozotocin)-diabetic rats. The neurons and Schwann cells do initiate protective mechanisms involving upregulation of antioxidant pathways; however, the neurodegenerative outcome is energy failure in the nerve, observed as a decrease in high energy intermediates (e.g. phosphocreatine), impaired axonal transport of proteins and sub-optimal ion pumping [1, 6] (Fig. 56.1).

Polyol pathway hyperactivity: Metabolic disorders are the primary cause of diabetic neuropathy. Hyperglycaemia, induced through decrease of insulin secretion or insulin resistance, is responsible for the enhancement of the polyol pathway activity. The rate-limiting first enzyme of this pathway, aldose reductase, catalyses the formation of sorbitol from glucose, with the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) to NADP+. Sorbitol is further oxidized to fructose by sorbitol dehydrogenase, which is coupled with the reduction of nicotinamide adenine dinucleotide (NAD+) to NADH. It is described that during hyperglycaemic states, the affinity of aldose reductase for glucose is higher, generating intracellular osmotic stress due to accumulation of sorbitol, since sorbitol does not cross cell membranes. Interesting, the nerve damage following the diabetic state seems not to be due to this osmotic stress since it has been reported insignificant sorbitol concentrations in the nerves of diabetic patients [7]. However, the current accepted hypothesis states that polyol pathway hyperactivity is pathogenic primarily by increasing the turnover of cofactors such as NADPH and NAD+, which leads to a decrease in the reduction and regeneration of glutathione, as well as to an increase of advanced glycation end product (AGE) production and activation of diacylglycerol and protein kinase C (PKC) isoforms. Depletion of glutathione could be the primary cause of oxidative stress and be related to the accumulation of toxic species [8]. In fact, aldose reductase inhibitors are effective in preventing the development of diabetic neuropathy in animal models, but they have demonstrated disappointing results and dose-limiting toxicity in human trials [7] (Figs. 56.1 and 56.2).

Oxidative stress and mitochondria: Hyperglycaemia induces activation of classical pathways like AGE, PKC, hexosamine and polyol pathways to mediate cellular damage [7]. Generation of superoxide from mitochondrial electron transport chain is known to contribute towards hyperglycaemia initiated various etiological pathways. Hyperglycaemia enhances the reducing equivalents to electron transport chain (ETC) and the electrochemical potential across the inner mitochondrial membrane and hence increases superoxide production [7]. Superoxide inhibits glyceraldehyde phosphate dehydrogenase (GAPDH) either directly or indirectly through PARP-mediated NADH+ depletion [10]. Inhibition of GAPDH by ROS leads to accumulation of glycolytic intermediates upstream of this enzyme and redirected to initiate cellular pathways like AGE formation. Once the AGEs are formed, they bind to RAGE and activate many other cru-

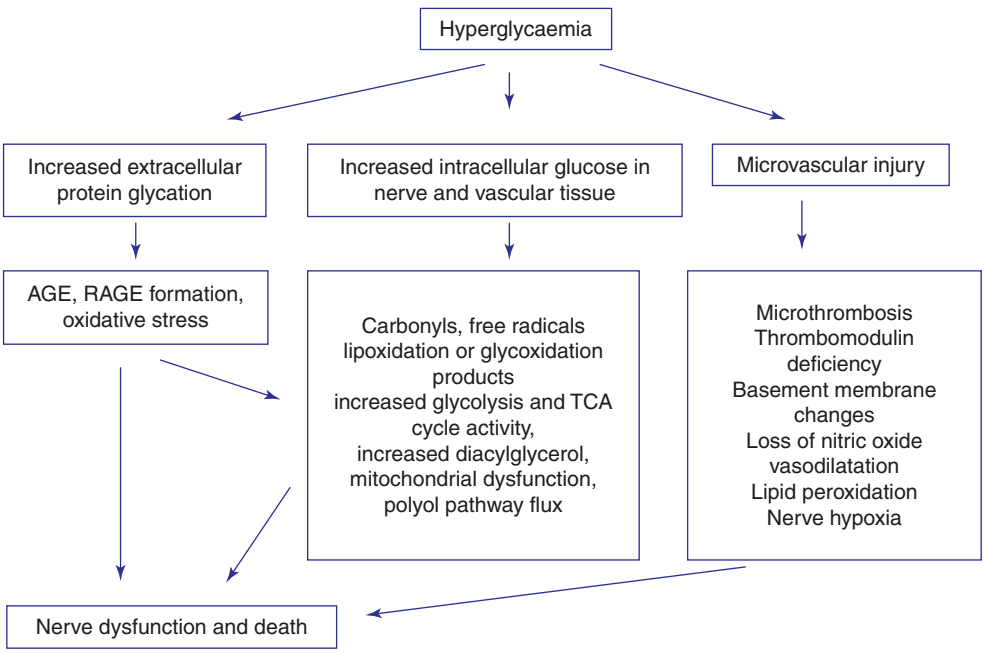

Fig. 56.1 The pathogenesis of diabetic neuropathy (Taken from Deli G et al. Diabetic neuropathies: diagnosis and management. Neuroendocrinology. 2013;98(4):267–80, ref. 1, with permission). *AGE* advanced glycation end product, *RAGE* receptors for AGEs, *TCA* tricarboxylic acid

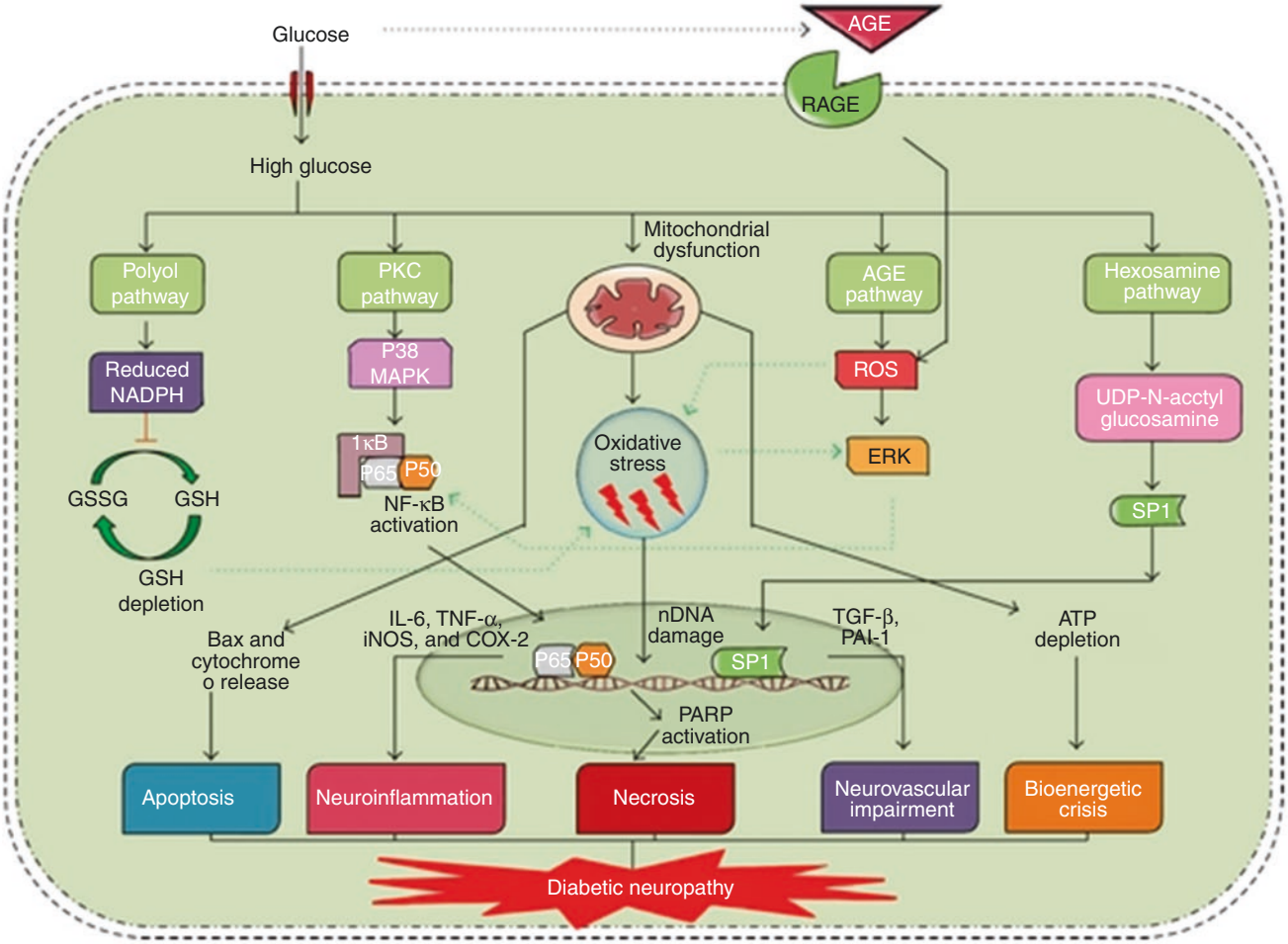

Fig. 56.2 Pathophysiology of diabetic neuropathy. Hyperglycaemia activates numerous metabolic pathways like polyol pathway, protein kinase c (PKC) pathway, advanced glycation end product (AGE) pathway and hexosamine pathway. All these pathways are known to integrate through hyperglycaemia-mediated mitochondrial ROS production. Oxidative stress and these classical pathways in combination activate transcription factors such as nuclear factor kappa enhancer of B cells (NF-κB) and speciality protein-1 (SP-1), resulting in neuroinflammation and vascular impairment. Further, these pathways combined with dysfunctional mitochondria-mediated apoptosis or bioenergetic depletion can lead to neuronal damage leading to DN. Poly-ADP ribose polymerase (PARP)-mediated NADH/ATP depletion can lead to neuronal dysfunction due to failure of various energy-dependent processes in neurons. (ERK, extracellular related kinase; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; TGF-β, transforming growth factor-β; and PAI-1, plasminogen activator inhibitor-1) (Taken from Sandireddy R et al. Neuroinflammation and oxidative stress in diabetic neuropathy: futuristic strategies based on these targets. Int J Endocrinol. 2014;2014:674987, ref. 9, with permission)

cial pathways like NF-κB and PARP. PKC pathway is activated through dihydroxyacetone phosphate-mediated diacylglycerol (DAG) activation. Hexosamine pathway is activated through enhanced flux of fructose-6-phosphate and polyol pathway by elevated glucose levels. This, in turn, leads to osmotic stress in the cells which further takes the cell towards necrotic cell death. Enhanced activity of Mn-SOD, a mitochondrial form of superoxide dismutase (SOD) or overexpression of uncoupling proteins (UCP-1) in experimental diabetic animals, prevents the development of vascular complications in the animals and also reduced oxidative stress-mediated neuronal damage. The mechanism for this neuroprotective effect can be the reduction of mitochondrial ROS generation and the clearance of the notorious ROS from the cells. In addition to the above theory, mitochondrial abnormalities and mitochondria-associated oxidative stress stand at a central position in the pathogenesis of diabetic neuropathy. It has been noticed that defects in functioning of ETC chain components compromise ATP production and enhance the generation of free radicals. The free radicals generated causes damage to mitochondrial DNA (mt DNA) and nuclear DNA (nDNA) which in turn aggravates mitochondrial damage. This vicious cycle developed inside mitochondria produces intense oxidative stress and drives the cell towards apoptotic/necrotic death. It is an established fact that diabetes is known to affect the respiratory capacity of ETC

functional complexes and thus alters ATP production (Fig. 56.1). Mainly complex I and complex III are known to be affected, which turns out to be electron leakage centres and thus inflates ROS production [7]. Various experimental observations point towards the critical role of mitotoxicity in the pathophysiology of diabetic neuropathy (Figs. 56.1 and 56.2).

Microvascular changes: DNP is frequently associated with microvascular impairment [1, 7]. In clinical and preclinical studies, it was found that peripheral perfusion is reduced, not only in the nervous tissue but also in the skin, being an important physiological evidence of microvasculature alteration. As a result, nerve ischaemia occurs, caused by raise in wall thickness and hyalinization of the basal lamina of vessels that nurse peripheral nerves, together with luminal reduction. These alterations are caused by plasma protein scape of capillary membrane to endoneurium, promoting swelling and augmented interstitial pressure in the nerves, accompanied by higher capillary pressure, deposition of fibrin and thrombus development. Hyperglycaemia per se can evoke nerve hypoxia, especially in sensory nerves, altering their electrical stability. Apparently controversial data from clinical studies described that diabetic patients suffering from the DNP presented higher levels of intravascular oxygen and augmented blood flow in the lower limbs than painless patients. As a result of nerve ischaemia, both diabetic patients and animals have shown a progressive nerve loss in proximal and distal segments, resulting in reduction of intraepidermal nerve fibre density. Consequently, axonal degeneration and regeneration also occur but more frequently in patients who do not experience pain. Besides axonal retraction and regeneration, another structural modification related to hyperglycaemia is myelin sheath alteration. The observed demyelinization can be related to Schwann cells' altered capacity to support normal myelin sheath [7] (Figs. 56.1 and 56.2).

Nerve excitability: Sensing ongoing spontaneous pain and paroxysmal shooting pain in the absence of any external stimulus is caused by ectopic impulse generation within the nociceptive pathways [1, 10]. The enhanced excitability can result from altered ion channel function, such as an increase in persistent sodium currents. Persistent sodium currents can be reliably estimated using threshold tracking. In peripheral neuropathy, persistent sodium currents usually increase possibly due to overexpression of sodium channels associated with axonal regeneration and could be responsible for ectopic firings. In diabetic neuropathy, the activation of the polyol pathway mediated by an enzyme, aldose reductase, leads to reduced Na(+)/K(+) pump activity and intra-axonal sodium accumulation; sodium currents are reduced presumably due to decreased trans-axonal sodium gradient [1, 10]. In addition to voltage-gated sodium channels, several other ion channels probably undergo alterations after a nerve lesion, such as voltage-gated potassium channels, which might also contribute to changes in membrane excitability of nociceptive nerves [1, 10] (Fig. 56.3).

Nerve injury also induces upregulation of various receptor proteins such as the transient receptor potential V1 (TRPV1), which is activated by heat at about 41 °C [1]. In neuropathic condition, TRPV1 is downregulated on affected/injured fibres but upregulated on uninjured C-fibres, thereby causing spontaneous nerve activity induced by normal body temperature.

Central sensitization: Central sensitization might develop as a consequence of ectopic activity in primary nociceptive afferent fibres, and structural damage within the CNS itself

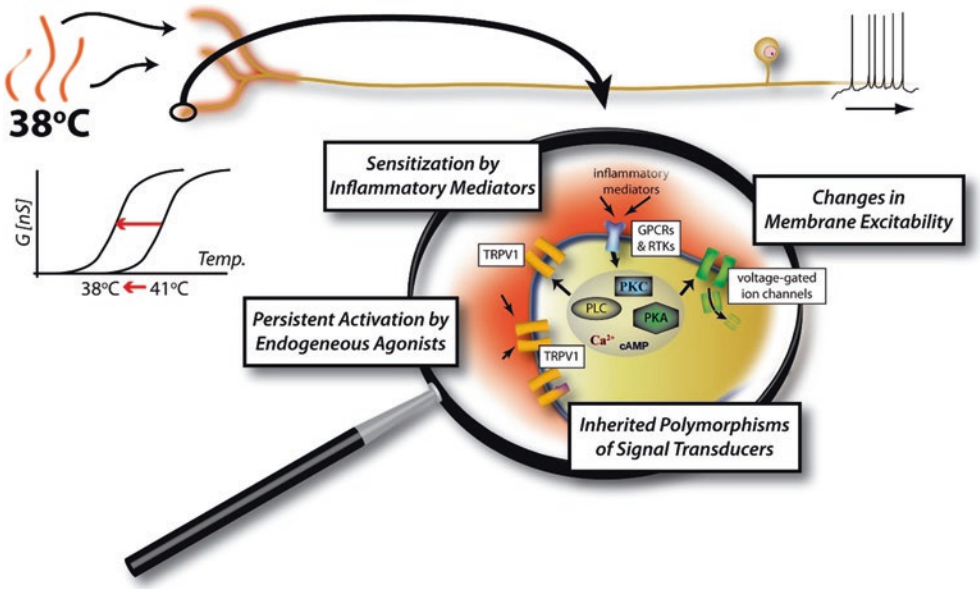

Fig. 56.3 Peripheral sensitization changes in the sensitivity of the peripheral terminals of nociceptors to stimuli can contribute to evoked pain. This can occur through inflammatory mediators sensitizing signal transducer proteins, persistent activation of transducer proteins by endogenous agonists, inherited polymorphisms of transducer proteins or an increase in membrane excitability. (Taken from von Hehn CA et al. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. Neuron. 2012;73(4):638–52, ref. 11 with permission)

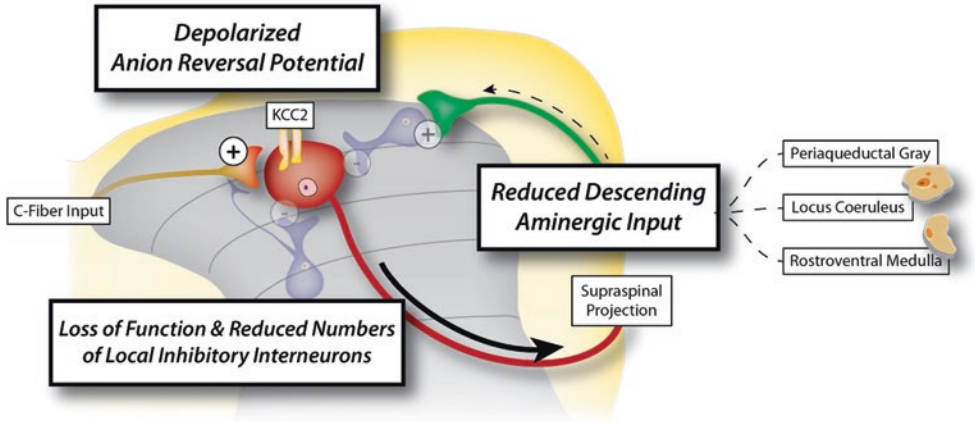

Fig. 56.4 Spinal disinhibition: Excitatory nociceptive signals are enhanced after nerve injury by a reduction in normal inhibitory regulation through a loss of local inhibitory interneurons, a depolarized anion reversal potential and reduced descending inhibition. (Taken from von Hehn CA et al. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. Neuron. 2012;73(4):638–52, ref. 11 with permission)

might not be necessarily involved. Spinal cord microglia are also strongly activated after nerve injury; the activated microglia not only exhibit increased expression of microglial markers CD 11 b and Iba 1 but also display elevated phosphorylation of p38 mitogen-activated protein kinase. Inhibition of spinal cord p38 has been shown to attenuate neuropathic and postoperative pain, as well as morphine-induced antinociceptive tolerance. Activation of p38 in spinal microglia results in increased synthesis and release of the neurotrophin brain-derived neurotrophic factor and the pro-inflammatory cytokines interleukin-1β, interleukin-6 and tumour necrosis factor-α. Phosphorylation of NMDA and AMPA receptors and expression of voltage-gated sodium channels are also involved both in the spinal cord and supraspinal structures. These mediators can powerfully modulate spinal cord synaptic transmission, leading to increased excitability of dorsal horn neurons, that is, central sensitization, partly via suppressing inhibitory synaptic transmission [1, 7, 10]. Further potent inhibitory neurons, such as descending pathways originating in the brainstem, contribute to modulation of pain processing. Lesions that affect these opioidergic and monoaminergic systems also lead to pain exacerbation via disinhibition [10] (Fig. 56.4).

'Chronic Pain Hurts the Brain'

The pain matrix is composed of several interacting networks. A nociceptive matrix receiving spinothalamic projections (mainly posterior operculoinsular areas) ensures the bodily specificity of pain and is the only one whose destruction entails selective pain deficits. Transition from cortical nociception to conscious pain relies on a second-order network, including posterior parietal, prefrontal and anterior insular areas. Second-order regions are not nociceptive-specific; focal stimulation does not evoke pain, and focal destruction does not produce analgesia, but their joint activation is necessary for conscious perception, attentional modulation and control of vegetative reactions. The ensuing pain experience can still be modified as a function of beliefs, emotions and expectations through activity of third-order areas, including the orbitofrontal and perigenual/limbic networks. The pain we remember results from continuous interaction of these subsystems, and substantial changes in the pain experience can be achieved by acting on each of them. Neuropathic pain (NP) is associated with changes in each of these levels of integration. The most robust abnormality in NP is a functional depression of thalamic activity, reversible with therapeutic manoeuvres and associated with rhythmic neural bursting. Neuropathic allodynia has been associated with enhancement of ipsilateral over contralateral insular activation and lack of reactivity in orbitofrontal/perigenual areas. Although lack of response of perigenual cortices may be an epiphenomenon of chronic pain, the enhancement of ipsilateral activity may reflect disinhibition of ipsilateral spinothalamic pathways due to depression of their contralateral counterpart. This in turn may bias perceptual networks and contribute to the subjective painful experience [12].

In addition to functional changes, morphological alterations at spinal and supraspinal levels have been reported in chronic pain. Neuropathic pain is accompanied by apoptosis of spinal cord cells, sprouting of nerve terminals in somatosensory cortex, grey matter density decrease in PFC associated with reduced cognitive abilities and thalamic atrophy. Morphometric analysis showed that chronic pain particularly in patients with a neuropathic pain component is associated with 5–10% of brain grey matter atrophy in the prefrontal cortex and thalamus. A decrease in grey matter was also

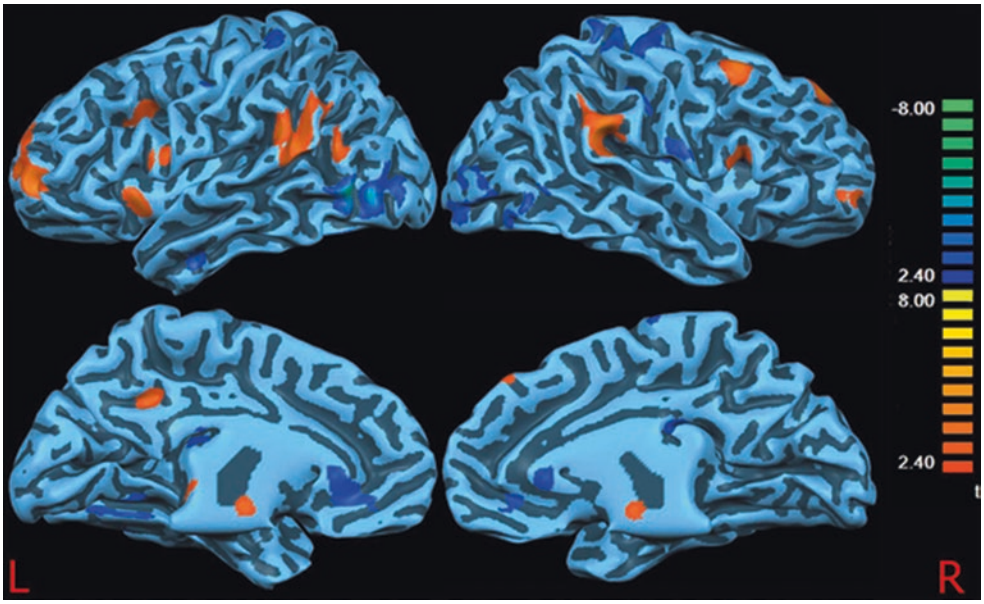

Fig. 56.5 DMN differences between controls and patients. Surface-rendered projection results of a two-sample t-test contrasting the default mode network in the healthy group vs. the pain group. The blue foci indicate the areas that showed significantly less correlational activity in the pain group than in the healthy group. Vice versa the yellow/red foci indicate the areas that showed significantly more correlational activity in the pain group than in the healthy group. (Taken from Cauda F et al. Altered resting state in diabetic neuropathic pain. PLoS One. 2009;4(2):e4542., ref. 13, with permission)

found in brainstem, temporal lobe and somatosensory cortex in addition to PFC in patients with chronic pain; cortical changes were more pronounced in the right hemisphere. It remains to be determined if reduced grey matter density is related exclusively or predominantly to a specific cell population (projection neurons, inhibitory interneurons and microglia) or if different cell types are affected equally. Nerve injury-induced apoptosis in the spinal dorsal horn caused a loss of GABAergic inhibitory interneurons and a decrease in inhibitory synaptic transmission. Microglia was hyperactivated at the spinal level after nerve injury but possibly inhibited in cortical areas in chronic pain [13].

In a revolutionary study by Cauda et al., functional connectivity analyses revealed a cortical network consisting of two anti-correlated patterns: one includes the left fusiform gyrus, the left lingual gyrus, the left inferior temporal gyrus, the right inferior occipital gyrus, the dorsal anterior cingulate cortex bilaterally and the pre- and postcentral gyrus bilaterally, in which its activity is correlated negatively with pain and positively with the controls; the other includes the left precuneus, dorsolateral prefrontal, frontopolar cortex (both bilaterally), right superior frontal gyrus, left inferior frontal gyrus, thalami, both insulae, inferior parietal lobuli, right mammillary body and a small area in the left brainstem, in which its activity is correlated positively with pain and negatively with the controls. Furthermore, a power spectra analysis revealed group differences in the frequency bands wherein the spatial independent component analysis (sICA) signal was decomposed: patients' spectra are shifted towards higher frequencies [14] (Fig. 56.5).

Ever since several studies have confirmed the role of central nervous system impairment. Both somatosensory pathways and cognition-related cerebral areas are involved based on functional MRI studies, which play a role in the complexity in the development of neuropathic pain and its emotional and mental consequences [15, 16]. Altered functional connectivity can also be detected in patients with type 1 diabetes mellitus [17].

Diagnosis

As it has been previously shown, prediabetes can also be associated with neuropathy. Based on the recent ADA (Americans with Disabilities Act) guidelines, diabetes can be diagnosed on the results of HgBA1C, fasting plasma glucose (FPG) or 2 h postprandial glucose (PG) levels. This statement recommended the use of the A1C test to diagnose diabetes, with a threshold of ≥6.5%. The established glucose criteria for the diagnosis of diabetes (FPG ≥ 7 mmol/l or 2h PG ≥ 11.1 mmol/l) remained valid as well [18].

Prediabetes can be defined as having impaired fasting glucose (IFG) (FPG levels 5.6–6.9 mmol/l) or impaired glucose tolerance (IGT) (2h PG values in the oral glucose tolerance test (OGTT) of 7.8–11.0 mmol/l). It should be noted that the World Health Organization (WHO) and a number of other diabetes organizations define the cutoff for IFG at 110 mg/dl (6.1 mmol/l) [1]. Hence, it is reasonable to consider an A1C range of 5.7–6.4% as identifying individuals with high risk for future diabetes, a state that may be referred to as prediabetes [1, 18]. As with glucose measurements, the continuum of risk is curvilinear—as A1C rises, the risk of diabetes rises disproportionately. Accordingly, interventions should be most intensive follow-up particularly vigilant for those with A1Cs above 6.0%, who should be considered to

be at very high risk. Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol and hypertension. The presence of prediabetes should prompt comprehensive screening for cardiovascular risk factors. Standards of lifestyle and medical care can also be found in this guideline [18].

In DPN, sensory deficits usually overshadow motor nerve dysfunction and appear first in the distal portions of the extremities and progress proximally in a 'stocking-glove' distribution with increasing duration or severity of diabetes [1]. In the typical form, the large nerve fibres are damaged later than the small ones [19]. The signs and symptoms of DPN vary depending on fibre type involved, with large fibre disease impairing proprioception and light touch. Small fibre disease impairs pain and temperature perception, leading to paresthesias, dysesthesias and/or neuropathic pain [2] (Table 56.1). Distal weakness occurs only in the most severe cases. Diminished or absent deep tendon reflexes, particularly the Achilles tendon reflex, often indicate mild and otherwise asymptomatic DPN. More advanced asymptomatic neuropathy may first present with late complications such as ulceration or neuroarthropathy (Charcot's joints) of the foot [1, 19].

For diagnosis of DN, bedside examination should include assessment of muscle power, sensations of pinprick, joint position, touch and temperature. Vibration test should be done by tuning fork of a 128 Hz. For touch sensation, mono filament of 1 g is recommended [1]. A number of questionnaires have been developed to help practitioners diagnose neuropathic pain [1, 9, 19]. The DN4 questionnaire is of particular interest, as it can be rapidly completed, is easy to use and has a good diagnostic performance: for a score ≥4/10, it has a sensitivity of 83% and a specificity of 90% for diagnosing neuropathic pain [9, 19]. The main advantage of screening tools is to identify potential patients with NP, particularly by non-specialists. However, these tools fail to identify 10–20% of patients with clinician-diagnosed NP, showing that they cannot replace careful clinical judgement [9] (Table 56.1).

Electrophysiological tests may have no place in the diagnosis of chronic sensorimotor diabetic neuropathy, as they can be normal when only small-diameter fibres are damaged, but are a reliable procedure in the case of mononeuropathies or radiculopathies to exclude any other etiology (demyelinating, toxic polyneuropathies, etc.). Such procedures should be performed only when the clinical presentation is atypical and the diabetic origin uncertain (asymmetrical symptoms or involvement of the upper limbs) [9, 19].

Among laboratory tests, laser-evoked potentials (LEPs) are the best tool for assessing Aδ pathway dysfunction (small-fibre neuropathy) and skin biopsy for assessing neuropathies with distal loss of unmyelinated nerve fibres [1, 9].

Table 56.1 Definition and assessment of negative and positive sensory symptoms and signs in patients with neuropathic pain (Taken from Deli G et al. Diabetic neuropathies: diagnosis and management. Neuroendocrinology. 2013;98(4):267–80, ref. 1, with permission)

Symptom	Sign	Assessment
Negative signs and symptoms		
Hypoesthesia Pallhypesthesia Hypoalgesia Thermohypoesthesia	Reduced sensation To non-painful stimuli To vibration To painful stimuli To cold or warm stimuli	Touch skin with Painter's brush, cotton swab Tuning fork Pinprick Objects of 10 and 45 °C
Spontaneous sensations/pain		
Paraesthesia Paroxysmal pain Superficial pain	Non-painful ongoing sensation Painful, shooting electrical attacks for seconds Painful ongoing sensation	Number per episode Grade intensity (0–10) Threshold for evocation Area in cm^2
Evoked pain		
Mechanical dynamic allodynia Mechanical static allodynia Mechanical punctate or pinprick hyperalgesia Temporal summation Cold allodynia Heat allodynia Mechanical deep somatic allodynia	Normally non-painful stimuli on skin evoke pain Normally non-painful pressure stimuli on skin evoke pain Normally stinging-but-not-painful stimuli evoke pain Repetitive application of identical single noxious stimuli is perceived as increasing pain sensation Normally non-painful cold stimuli evoke pain Normally non-painful heat stimuli evoke pain Normally non-painful pressure on deep somatic tissues evokes pain	Stroking skin with painter's brush etc. Manual gentle mechanical pressure to the skin Manual gentle pricking of the skin Pricking the skin with safety pin at <3 s intervals for 30 s Touch skin with objects of 20 °C Touch skin with objects of 40 °C Manual light pressure at joints or muscle

Forms of Diabetic Neuropathy

Several fairly distinct clinical syndromes of diabetic neuropathy have been delineated: the most common as noted is a distal, symmetrical, primarily sensory polyneuropathy affecting feet and legs in a chronic, slowly progressive manner; the others are acute ophthalmoplegia that affects the third and less often the sixth cranial nerve on one side; acute mononeuropathy of limbs or trunk including a painful thoracolumbar radiculopathy; an acute or subacute painful, asymmetrical, predominantly motor multiple neuropathy affecting the upper lumbar roots and the proximal leg muscles ('diabetic amyotrophy'); a more symmetrical, proximal motor weakness and wasting, usually without pain and with variable sensory loss, pursuing a subacute or chronic course; and an autonomic neuropathy involving bowel, bladder, sweating and circulatory reflexes. These forms of neuropathy often coexist or overlap, particularly the autonomic and distal symmetrical types and the subacute proximal neuropathies (Tables 56.2 and 56.3).

Table 56.2 The main features of different patterns of disabling neuropathies in patients with diabetes (Taken from Deli G et al. Diabetic neuropathies: diagnosis and management. Neuroendocrinology. 2013;98(4):267–80, reference 1, with permission)

	Pains	Distal symmetrical sensory loss	Weakness	Sensory ataxia	Autonomic dysfunction	Progression	CSF protein	Electrophysiological test	Nerve biopsy
Length-dependent polyneuropathy	Frequent in distal limbs	Length dependently predominates on pain and temperature sensations	Minor, distal symmetrical	Rare	Common	Years	Variable	Axonal pattern, distal symmetrical	Massive axonal loss
CIDP in diabetic patients	Occasional	Variable predominates on proprioception	Common, often severe proximal and distal	Common	Uncommon	Weeks or months	Increased	Mixed axonal and demyelinative	Variable axon loss and demyelination
Focal/multifocal diabetic neuropathy	Present in most cases	Variable	Common—asymmetrical—nerve or root territory	Uncommon	Uncommon	Weeks or months	Increased	Axonal pattern, multifocal	Variable

CIDP chronic inflammatory demyelinating polyneuropathy, *CSF* cerebrospinal fluid

Table 56.3 First-line treatment of neuropathic pain (Taken from Deli G et al. Diabetic neuropathies: diagnosis and management. Neuroendocrinology. 2013;98(4):267–80, reference 1, with permission)

Drug	Mode of action	Cautions	Major side effects	Other benefits	NNT	NNH	NNMH
TCA	Inhibition of reuptake of serotonin and/or norepinephrine, block of sodium channels, anticholinergic	Postinfarct states and arrhythmias	Sedation and anticholinergic effects	Improvement of depression and sleep disturbance	1.3–2.4	2.7–6	15–28
SNRI	Inhibition of both serotonin and norepinephrine reuptake	Hepatic dysfunction, renal insufficiency, alcoholism and cardiac disease	Nausea	Improvement of depression	3.1–6	9.6	17–21
Gabapentine	Decreases release of glutamate, norepinephrine and substance P, with ligands on α2-δ subunit of voltage-gated calcium channel	Renal insufficiency	Sedation, dizziness and peripheral oedema	No clinically significant drug interactions	3.3–5.8	2.7–3.7	11–23
Pregabalin	See above	See above	See above	See above plus improvement of sleep disturbance and anxiety	2.9–5	3.7	11–23
Opioids	μ-Receptor agonism, inhibition of norepinephrine and serotonin reuptake	History of substance abuse, suicide risk, driving impairment, concomitant use of SSNRI and tricyclic antidepressant (serotonin syndrome)	Nausea/vomiting, constipation and dizziness	No systemic side effects and rapid onset of analgesic effect	2.6–4.3	3.6	7.8

TCA tricyclic antidepressant, *SNRI* serotonin and norepinephrine reuptake inhibitor, *NNT* number needed to treat, *NNH* number needed to harm, *NNMH* number needed to major harm

Sensorimotor Neuropathy

Distal sensory diabetic polyneuropathy: This is the most common presentation of neuropathy in diabetes, and up to 50% of patients may experience symptoms, most frequently burning pain, electrical or stabbing sensations, paresthesia, hyperesthesia and deep aching pain [1]. These symptoms are generally worse at night and disturb sleep. Together with painful symptoms during the day, this often leads to a reduction in individual's ability to perform daily activities [11].

Examination of the lower limb usually reveals sensory loss of vibration, pressure, pain and temperature perception (mediated by small and large fibres) and absent ankle reflexes [15–17]. Muscle weakness is usually mild, but in some patients, a distal sensory neuropathy is combined with a proximal weakness and wasting [1, 9, 11, 19].

Interestingly, as up to half of the patients may be asymptomatic, a diagnosis may only be made on examination or, in some cases, when the patient presents with a painless foot ulcer [1].

About 10% of diabetic patients experience persistent pain (so-called painful diabetic neuropathy) [11]. Some patients develop predominantly small fibre neuropathy manifesting with pain and paresthesia early in the course of diabetes that may be associated with insulin therapy (insulin neuritis) [8, 20].

Acute diabetic mononeuropathies: Cranial neuropathy in diabetic patients most commonly involve the oculomotor nerve followed by trochlear and facial nerve in order of frequency. Third nerve palsy with pupillary sparing is the hallmark of diabetic oculomotor palsy and is attributed to nerve infarction [8, 9, 11, 19, 21].

Isolated involvement of practically all the major peripheral nerves has been described in diabetes (e.g. carpal tunnel syndrome (CTS) is three times more common in diabetic patients than the normal population and CTS is the second most common neuropathic disease in diabetic patients), but the ones most frequently affected are the femoral, sciatic and peroneal nerves, in that order [22–25]. Rarely is a nerve in the upper extremity affected. In these cases, nerve entrapment seems to be commoner than nerve infarction [8, 9, 11, 19].

The mononeuropathies often emerge during periods of transition in the diabetic illness, for example, after an episode of hyper- or hypoglycaemia, when insulin treatment is initiated or adjusted or when there has been rapid weight loss [1, 8, 9, 11, 19].

Diabetic multiple mononeuropathies and radiculopathies: This category overlaps with the mononeuropathies. A syndrome of painful unilateral or asymmetrical multiple neuropathies tends to occur in older patients with relatively mild or even unrecognized diabetes. Multiple nerves are affected in a random distribution (mononeuritis multiplex). As in mononeuropathy, the onset is abrupt in one nerve and occurs earlier than the other nerves, which are involved sequentially or irregularly. Nerve infarctions occur because of occlusion of vasa nervosum and should be differentiated from systemic vasculitis [8, 9, 11, 19].

Characteristic diabetic syndromes present subacutely with pain followed by weakness, which affect primarily patients with mild diabetes called radiculoplexus neuropathies (Table 56.3). Three main types can occur, alone or in combination, and include diabetic cervical radiculoplexus neuropathy (DCRPN), diabetic thoracic radiculoneuropathy (DTRN) and diabetic lumbosacral radiculoplexus neuropathy (DLRPN) [8, 9, 11, 19].

Diabetic lumbosacral radiculoplexus neuropathy (DLRPN) occurs in approximately 1% of diabetic patients and probably is the form of diabetic neuropathy that causes the most morbidity [25]. It has been variably known by different names, including diabetic amyotrophy, Bruns-Garland syndrome, diabetic mononeuritis multiplex, diabetic polyradiculopathy, proximal diabetic neuropathy and others [1]. Pain, which can be severe, begins in the low back or hip and spreads to the thigh and knee on one side; the discomfort has a deep, aching character with superimposed lancinating jabs, and there is a propensity for pain to be most severe at night. Although pain is initially the worse symptom, weakness and atrophy become the main problem, which are mainly evident in the pelvic girdle and thigh muscles, although the distal muscles of the leg may also be affected [8, 19].

Diabetic thoracic radiculopathies are a rare but important complication of diabetes mellitus. These typically present with severe pain and dysesthesias along the trunk, chest or abdominal wall and often prompt extensive workups for underlying chest or abdominal pathology [1]. They can be symmetric and can involve multiple dermatomes [8, 9, 11, 19]. While DLRPN is a much more familiar branch of the DRPN spectrum, the cervical segment can also be involved, but it is very rare [8].

Insulin neuritis: In a seemingly paradoxical relationship, both poor glucose control and rapid treatment of hyperglycaemia can be associated with an increased risk of neuropathy. A clinically distinct form of neuropathy that deserves mention is treatment-induced neuropathy in diabetes (TIND). This underdiagnosed iatrogenic small-fibre neuropathy is defined as the acute onset of neuropathic pain and/or autonomic dysfunction within eight weeks of a large improvement in glycaemic control specified as a decrease in glycosylated HbA1c of more than 2% points over 3 months [8]. TIND was first recognized soon after the introduction of insulin and named 'insulin neuritis' [1, 8, 20–22]. For many decades, 'insulin neuritis' was considered a rare cause for acute neuropathy. However, recently published data suggest that it is much more common and clinically relevant. It is most common in type 1 diabetes mellitus (DM) treated with

insulin, although rapid glucose correction can occur in both types of diabetes as a result of either insulin or less frequently oral agents. In a study by Gibbons and Freeman, a surprising 10.9% of 954 subjects with diabetes met criteria for TIND, and the risk of developing TIND was associated with the magnitude and rate of HbA1c change [20]. Similar to DPN, the neuropathy of TIND generally follows a length-dependent pattern, but, in contrast, the pain and autonomic symptoms are more extensive and less responsive to opioids. The underlying pathophysiology is poorly understood, although it has been suggested that rapid glycaemic control both with and without insulin leads to hemodynamic changes (arteriovenous shunting) resulting in endoneurial hypoxia of small fibres [8, 20–22].

Diabetes-Associated Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Chronic inflammatory demyelinating polyneuropathy (CIDP), as the name implies, is an autoimmune disorder of unknown etiology in two-thirds of the patients; however, in remaining one-third, an etiological cause might be found. Some currently described etiologies include gammopathies including monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, Castleman's disease and Waldenstrom gammopathy; also, other concurrent disorders like inflammatory bowel disorders, cutaneous melanoma and Hodgkin's lymphoma have been implied [23]. CIDP has typical and atypical phenotypic variants. Only half of CIDP patients have typical CIDP, which exhibits symmetrical sensory and motor symptoms. The remainder has atypical disease, which presents with predominantly focal, sensory, motor, distal or asymmetrical symptoms. Despite increased efforts to identify a biomarker, there is no definitive diagnostic marker for CIDP, and recognition of CIDP is not straightforward in some cases due to its heterogeneous nature [24]. For further details, see the excellent review by Nelligan et al. [25].

Simultaneous occurrence of CIDP and diabetes mellitus (DM) (diabetic CIDP or CIDP-DM) is frequently seen in clinical practice; however, it is ambiguous whether the two disorders are pathogenetically correlated. It is of utmost importance to be familiar with CIDP occurring in diabetics for the reason that contrasting to diabetic polyneuropathy, it may be treatable [23].

There is an increasing body of literature suggesting that the prevalence of CIDP tends to be higher in diabetic patients, especially in those of older age. A recent retrospective health insurance administrative claims database study suggested that the prevalence of CIDP in a nondiabetic population is 6 per 100,000 persons, while the prevalence of CIDP in a patient population with DM is ninefold higher at 54 per 100,000 persons. The association of CIDP with DM remains controversial, as both diseases have increased prevalence in patients over age 50 years. It is a challenge to identify CIDP in a diabetic population due to concomitant axonal damage. Although some patients with CIDP and DM respond to treatment, it is difficult to predict response. Because of the rising prevalence of DM throughout the world, there is a need to differentiate CIDP from DPN accurately [24].

The diagnosis of CIDP relies on a combination of clinical and electrophysiological criteria. A number of criteria have been proposed. The European Federation of Neurological Societies (EFNS)/Peripheral Nerve Society (PNS) guidelines were developed for clinical and research use [26]. The criteria combine clinical features and electrophysiological evidence to define CIDP, with supportive criteria including elevated cerebrospinal fluid (CSF) protein, gadolinium enhancement of nerve roots or plexus on MRI or nerve biopsy findings providing supplemental diagnostic evidence. Electrodiagnostic evidence of peripheral nerve demyelination in motor nerves is required for diagnosis, including distal latency prolongation, reduction of motor conduction velocity, prolongation of F-wave latency and partial motor conduction block, and must be identified in at least two nerves for a diagnosis of 'definite' CIDP. It should be noted that in some cases of pure sensory CIDP where routine motor conduction studies are normal, the EFNS/PNS guidelines may fail to diagnose the condition as CIDP. In these cases, if CIDP is suspected, the proximal region of the peripheral sensory nervous system should be carefully interrogated using sensory-evoked potentials. Although other criteria have been proposed, the EFNS/PNS criteria have good sensitivity and specificity for CIDP diagnosis and are currently the most commonly used [26].

Treatment of Diabetic Neuropathy

In diabetic patients, the risk of DPN and autonomic neuropathy can be reduced with improved blood glucose control, and the improvement of lipid and blood pressure indexes and the avoidance of cigarette smoking and excess alcohol consumption are already recommended for the prevention of other complications of diabetes [1].

Preventive Treatment

Based on the etiology of diabetic neuropathy, several agents have been tested to halt its progression (after the onset of subjective symptoms, only palliative treatments are currently available), thereby improving clinical outcome [23]. A very recent meta-analysis showed that main preventive strategies for DPN are intensive glycaemic control with a target

HbA1c < 6% in patients with type 1 diabetes mellitus and standard control of 7.0–7.9 in patients with type 2 diabetes mellitus, incorporating lifestyle modifications.

An analysis of the literature on experimental peripheral diabetic neuropathy suggests that, to date, all of the pharmacological agents shown to counteract one or several manifestations of painful or insensate neuropathy also have efficacy against nerve conduction velocity deficit [27]. Animal studies using pharmacological and genetic approaches revealed important roles of increased aldose reductase, protein kinase C and poly(ADPribose) polymerase activities, advanced glycation end products and their receptors, oxidative-nitrosative stress, growth factor imbalances and C-peptide deficiency in both painful and insensate neuropathies [27].

Aldose reductase inhibitor treatment was suggested not only improving impaired conduction velocity but also improving a variety of subjective symptoms based on recent studies [24]. These findings may support the hypothesis that the polyol pathway plays a central role in the onset and progress of diabetic neuropathy in human subjects. On the other hand, a Cochrane meta-analysis including 32 trials found no overall significant difference between the treated and control groups (SMD -0.25, 95% CI -0.56 to 0.05), although one subgroup analysis (four trials using tolrestat) is favoured [28]. There was no overall benefit on nerve conduction parameters (27 studies) or foot ulceration (one study). Quality of life was not assessed in any of the studies. While most adverse events were infrequent and minor, three compounds had dose-limiting adverse events that lead to their withdrawal from human use: severe hypersensitivity reactions with sorbinil, elevation of creatinine with zenarestat and alteration of liver function with tolrestat [28]. Interestingly, they may ameliorate cardiac automatic neuropathy especially mild or asymptomatic forms, but it merits further investigations as randomized trials are lacking [29].

Alpha lipoic acid is also a potent antioxidant in experimental models, reported to reduce diabetic microvascular and macrovascular complications in animal models [30]. Four trials (ALADIN I, ALADIN III, SYDNEY, NATHAN II) comprised $n = 1258$ patients (α-lipoic acid $n = 716$; placebo $n = 542$) were included in the first meta-analysis based on the intention-to-treat principle. The results of this meta-analysis provided evidence that treatment with α-lipoic acid (600 mg/day i.v.) over three weeks is safe and significantly improves both positive neuropathic symptoms and neuropathic deficits to a clinically meaningful degree in diabetic patients with symptomatic polyneuropathy [30]. This statement was also included in the ADA guidelines as a Level I, Grade A evidence [1]. On the other hand, this meta-analysis did not fulfil the requirements of the Cochrane Collaboration [30]. In an economical point of view, standard symptomatic treatment seems to be much more cheaper in Europe [1, 30]. The combination of parenteral (600 mg daily for three weeks) and oral therapy (600 mg three times daily for six months) administered over a total of seven months failed to translate into significant improvements [1]. The four-year-follow-up Nathan 1 trial also led to this neutral result [1, 30]. A recent meta-analysis confirmed the abovementioned findings [1, 30]. The current AAN (American Academy of Neurology) and EFNS (European Federation of Neurological Societies) guidelines do not support the use of this drug in neuropathic conditions [1].

Angiotensin-converting enzyme (ACE) or angiotensin receptor blockers (ARB) are widely used in diabetic patient to manage blood pressure and prevent or treat cardiovascular disease and nephropathy. Large-scale studies of the effects of ACE inhibitors or ARBs have not been done, although some small studies and prospective assessments have been performed with positive impact on neuropathy [1].

Symptomatic Treatment: Painful Diabetic Neuropathy

Tricyclic antidepressants (TCA): These are so-called early antidepressant medications. These first-generation medications were effective in the treatment of depression because they enhanced serotonergic or noradrenergic mechanisms or both. They also were the first medication category that proved effective for neuropathic pain in placebo-controlled trials [26]. Unfortunately, the TCAs also blocked histaminic, cholinergic and alpha1-adrenergic receptor sites, and this action brought about unwanted side effects such as weight gain, dry mouth, constipation, drowsiness and dizziness [30]. The cardiovascular effects of TCAs are well characterized and include orthostatic hypotension, slowed cardiac conduction, type 1A antiarrhythmic activity and increased heart rate. Although much of them are temporary and exhibit mild effect, they are generally well tolerated. Based on a Cochrane analysis for diabetic neuropathy, the number needed to treat (NNT) for effectiveness was 1.3 (95% CI 1.2 to 1.5), the number needed to harm (NNH) for minor adverse effects was 6 (95% CI 4.2 to 10.7) and number needed to harm (NNH) for major adverse effects defined as an event leading to withdrawal from a study was 28 (95% CI 17.6–68.9) [31]. Comparison meta-analysis of TCAs and SSRIs showed beneficial safety profiles (but the key effects differed between the drug classes) [1, 31]. On the other hand, their use should be avoided in post-infarct states and in the case of conduction disturbances and cardiac arrhythmias (IA antiarrhythmic effect) [1] (Table 56.3).

Selective serotonin reuptake inhibitors (SSRIs): The SSRIs are increasingly being used to treat a spectrum of depressed patients, including the elderly. As a class, SSRIs have comparable efficacy to TCAs against depression but are generally better tolerated [31]. Despite of their widely use,

there is still limited evidence for the role of classical SSRIs in the treatment of painful diabetic neuropathy [31].

The class of serotonin and norepinephrine reuptake inhibitors (SNRIs) now comprises three medications: venlafaxine, milnacipran and duloxetine. These drugs block the reuptake of both serotonin (5-HT) and norepinephrine with differing selectivity. Whereas milnacipran blocks 5-HT and norepinephrine reuptake with equal affinity, duloxetine has a tenfold selectivity for 5-HT and venlafaxine a 30-fold selectivity for 5-HT. All three SNRIs are efficacious in treating a variety of anxiety disorders [32–34].

Venlafaxine (three studies) has an NNT of 3.1 (95% CI 2.2–5.1). The NNH for minor adverse effects 9.6 (95% CI 3.5 to 13) and the number needed to harm (NNH) for major adverse effects defined as an event leading to withdrawal from a study 16.2 (95% CI 8–436) for venlafaxine [1].

Duloxetine at 60 mg daily was also effective in treating painful diabetic peripheral neuropathy in the short term to 12 weeks with a risk ratio (RR) for 50% pain reduction at 12 weeks of 1.65 (95% confidence interval (CI) 1.34–2.03) and number needed to treat (NNT) 6 (95% CI 5–10) [32–34]. In a side effect analysis, it was generally safe and well tolerated, with the three most commonly reported adverse events which were nausea, somnolence and constipation. Modest changes in glycaemia were associated with duloxetine. Aspartate transaminase/alanine transaminase increases were transient and not considered predictive of more severe outcomes [33, 34] (Table 56.3).

Antiepileptic drugs: Antiepileptic drugs (AEDs) have a long history of effectiveness in the treatment of neuropathic pain, dating back to case studies of the treatment of trigeminal neuralgia with phenytoin in 1942 and carbamazepine in 1962 [1, 35–38]. Since 1993, nine new AEDs (felbamate, gabapentin, pregabalin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine and zonisamide) have received Food and Drug Administration (FDA) approval for the adjunctive treatment of partial seizures [35–38]. In addition to providing efficacy against epilepsy, these new AEDs may also be effective in neuropathic pain. For example, spontaneous activity in regenerating small caliber primary afferent nerve fibres may be quelled by sodium channel blockade, and hyperexcitability in dorsal horn spinal neurons may be decreased by the inhibition of glutamate release [35–38].

Gabapentin is an effective agent in the treatment of diabetic neuropathy, the NNT for effective pain was 2.9 (95% CI 2.2 to 4.3) and the NNH for minor harm was 3.7 (95% CI 2.4 to 5.4). Persons taking gabapentin can expect to suffer dizziness (21%), somnolence (16%), peripheral oedema (8%) and gait disturbance (9%). Serious adverse events (4%) were no more common than with placebo [35–38] (Table 56.3).

Pregabalin at doses of 300 mg, 450 mg and 600 mg daily was effective in patients with postherpetic neuralgia, painful diabetic neuropathy, central neuropathic pain and fibromyalgia (19 studies, 7003 participants). Pregabalin at 150 mg daily was generally ineffective [1]. The best (lowest) NNT for each condition for at least 50% pain relief over baseline (substantial benefit) for 600 mg pregabalin daily compared with placebo were 5.0 (4.0–6.6) for painful diabetic neuropathy. With 600 mg pregabalin, daily somnolence typically occurred in 15–25% and dizziness occurred in 27–46%. The proportion of participants reporting at least one adverse event was not affected by dose nor was the number with a serious adverse event, which was not more than with placebo [35–38] (Table 56.3).

The efficacy of valproic acid and lamotrigine is doubtful; they are not recommended routinely [32]. Using the Cochrane criteria, carbamazepine seems to be effective; on the other hand, no trial was longer than 4 weeks, of good reporting quality, using outcomes equivalent to at least moderate clinical benefit. In these circumstances, caution is needed in interpretation, and meaningful comparison with other interventions is not possible [1, 35–38]. The efficacy of topiramate is also neutral in this condition [1, 35–38].

Narcotic agents: Short-term studies provide only equivocal evidence regarding the efficacy of opioids in reducing the intensity of neuropathic pain, whereas intermediate-term studies demonstrate significant efficacy of opioids over placebo, which is likely to be clinically important [39]. The opioids studied were classified as weak (tramadol, propoxyphene, codeine) or strong (morphine, oxycodone) [39]. Weak and strong opioids outperformed placebo for pain and function in all types of neuropathic pain based on the result of a recent meta-analysis [39]. Other drugs produced better functional outcomes than opioids, whereas for pain relief, they were outperformed only by strong opioids. Dropout rates averaged 33% in the opioid groups and 38% in the placebo groups [39]. Among the side effects of opioids, only constipation and nausea were clinically and statistically significant.

Benzodiazepines: Agonists at the benzodiazepine binding site of ionotropic gamma-aminobutyric acid (GABA(A)) receptors are in clinical use such as hypnotics, anxiolytics and anticonvulsants since the early 1960s. Analgesic effects of classical benzodiazepines have occasionally been reported in certain subgroups of patients suffering from chronic pain or after spinal delivery through intrathecal catheters. However, these drugs are generally not considered as analgesics. Recent evidence from genetically modified mice now indicates that agents targeting only a subset of benzodiazepine (GABA(A)) receptors should provide pronounced antihyperalgesic activity against inflammatory and neuropathic pain. Several such compounds have been developed recently, which exhibit significant antihyperalgesia in mice and rats and appear to be devoid of the typical side effects of classical benzodiazepines [40].

Other agents: Local lidocaine and capsaicin cream have been shown to be effective in the treatment of neuropathic

conditions. They are included as potential therapeutic options in the recent AAN guidelines. Acupuncture, but not traditional Chinese herbal medicine, seems to be slightly effective. Transcutaneous electric nerve stimulation (TENS) should also be considered in the treatment of painful diabetic neuropathy [1].

Comparison: In random effect and fixed effect analyses of duloxetine (DLX), pregabalin (PGB) and gabapentin (GBP), all were superior to placebo for all efficacy parameters, with some tolerability trade-offs. Indirect comparison of DLX with PGB found no differences in 24 h pain severity, but significant differences in subjective global improvement, favouring PGB, and in dizziness, favouring DLX, were apparent. Comparing DLX and GBP, there were no statistically significant differences [41]. In three head-to-head trials, there was no difference between gabapentin and tricyclic antidepressants for achieving pain relief (RR 0.99, 95% CI 0.76 to 1.29) [42]. In a recent network meta-analysis, all interventions remained effective in comparison with placebo (mean difference in change of pain from baseline compared with placebo, amitriptyline, -12.58 [95% CI -16.66 to −8.50]; capsaicin, -9.40 [95% CI -13.92 to −4.88]; gabapentin, -10.22 [95% CI -17.25 to −3.19]; and pregabalin, -10.53 [95% CI -14.74 to −6.32] [35–37]. Based on these results, 5% lidocaine medicated plaster was comparable with the previously mentioned medications [43].

The recent ADA guidelines recommend optimization of glucose control to prevent or delay the development of neuropathy in patients with type 1 diabetes and to slow the progression of neuropathy in patients with type 2 diabetes [44]. Pregabalin, duloxetine are gabapentin are the first line of pharmacological treatments for painful diabetic neuropathy [44]. A very recent narrative in-depth review included pregabalin and duloxetine as first-line treatment options (and gabapentin as a reasonable alternative to pregabalin). Second- and third-line drugs were opioids (they are effective but adverse reactions and addiction concerns should be kept in mind) and topical analgesics. Pathogenesis-oriented treatments such as α-lipoic acid and actovegin should be confirmed in more extensive trials [45].

Combination therapy: Unfortunately there are too few controlled studies (complying with modern requirements for EBM) on combination therapy for neuropathic pain (84). Based on pharmacological, and pharmacokinetical profile, SNRIs and TCAs cannot be combined because of the high possibility of serotonin syndrome. TCAs and gabapentin and pregabalin or SNRI in combination with the abovementioned agents are good possibilities. Opioids can be combined with each of these drugs. Based on the recent AAN guidelines, venlafaxine may be added to gabapentin for a better response, and the EFNS guidelines prefer the combination therapy of TCA-gabapentin and gabapentin-opioids [1].

The recently published COMBO-DN multicentre, double-blind, parallel-group study in diabetic peripheral neuropathic pain addressed whether, in patients not responding to standard doses of duloxetine or pregabalin, combining both medications is superior to increasing each drug to its maximum recommended dose [46]. For initial eight-week therapy, either 60 mg/day duloxetine (groups 1 and 2) or 300 mg/day pregabalin (groups 3 and 4) was given. Thereafter, in the eight-week combination/high-dose therapy period, only nonresponders received 120 mg/day duloxetine (group 1), a combination of 60 mg/day duloxetine and 300 mg/day pregabalin (groups 2 and 3) or 600 mg/day pregabalin (group 4). Eight hundred four patients were evaluated for initial therapy and 339 for combination/high-dose therapy. Fifty percent response rates were 52.1% for combination and 39.3% for high-dose monotherapy ($P = 0.068$). In exploratory analyses of the initial eight-week therapy uncorrected for multiple comparisons, 60 mg/day duloxetine was found superior to 300 mg/day pregabalin ($P < 0.001$) [46]. Although not significantly superior to high-dose monotherapy, combination therapy was considered to be effective, safe and well tolerated.

Low-quality evidence raised the possibility of the combination of oxycodone with pregabalin and that of pregabalin with the 5% lidocaine plaster, but future, clear-cut studies are required to drive evidence-based decisions in the clinical setting [47].

Multiple Choice Questions

1. Consequences of peripheral diabetic neuropathy:
   (a) Morbidity
   (b) Discapacity
   (c) Mortality
   (d) Diminished quality of life
   (e) **All of the above**
2. Prevalence of peripheral neuropathy in patients with prediabetes:
   (a) Zero, it is exclusive of patients with diabetes
   (b) 5–10%
   (c) **11–25%**
   (d) 26–40%
   (e) 41–55%
3. Key pathological process inducing nerve damage in diabetes:
   (a) Trauma
   (b) **Oxidative stress**
   (c) Ischaemia
   (d) All of the above
   (e) None of the above
4. Diabetic peripheral neuropathy initially affects:
   (a) One extremity
   (b) Several extremities, asymmetrically
   (c) The proximal portions of the extremities
   (d) **The distal portions of extremities, symmetrically**
   (e) The distal portions of extremities, asymmetrically

5. The percentage of patients with asymptomatic distal sensory diabetic neuropathy is:
   (a) 100%
   (b) 75%
   (c) **50%**
   (d) 25%
   (e) 10%
6. Acute diabetic mononeuropathies are frequently associated:
   (a) With adequate metabolic control
   (b) With viral infections
   (c) With emotional stress
   (d) **With periods of transitions of the disease**
   (e) None of the above
7. Effective doses of pregabalin for the treatment of painful diabetic neuropathy:
   (a) 75 mg/day
   (b) 150 mg/day
   (c) **300 mg/day**
   (d) **450 mg/day**
   (e) **600 mg/day**
8. Traditional benzodiazepines are effective analgesics.
   (a) True
   (b) **False**
9. The evidence regarding the efficacy of opioids in reducing the intensity of neuropathic pain shows that:
   (a) They should be standard therapy.
   (b) They are superior to tricyclic antidepressants.
   (c) They are equally effective to pregabalin.
   (d) **They are only superior to placebo, and the evidence is equivocal**.
   (e) They should not be used.
   (f) They are equally effective to non-steroid anti-inflammatories.
10. In patients with diabetic peripheral pain, the COMBO-DN study showed:
   (a) That combination therapy with duloxetine and pregabalin is superior to high dose monotherapy
   (b) That 300 mg pregabalin is superior to 60 mg duloxetine
   (c) **That 60 mg duloxetine is superior to 300 mg pregabalin**
   (d) That both medications have similar rates of effectiveness and safety
   (e) That doses of duloxetine could be decreased

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Diabetic Cardiac Autonomic Neuropathy

57

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Abbreviations

ABPM	Ambulatory blood pressure monitoring
BP	Blood pressure
BRS	Baroreflex sensitivity
CAD	Coronary artery disease
CAN	Cardiac autonomic neuropathy
CARTs	Cardiovascular autonomic reflex tests
CHD	Coronary heart disease
CVD	Cardiovascular diseases
DLP	Dyslipidemia
DM	Diabetes mellitus
GLP1-RA	Glucagon-like peptide 1 receptor agonists
HR	Heart rate
HRT	Heart rate turbulence
HRV	Heart rate variability
LV	Left ventricular
MI	Myocardial infarction
MSNA	Muscle sympathetic nerve activity
OH	Orthostatic hypotension
QTi	QT interval
SGLT2i	Sodium glucose transporter 2 inhibitors
SMI	Silent myocardial ischemia
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
α-LA	α-Lipoic acid
ω-3 PUFA	ω-3 Polyunsaturated fatty acids

Core tip: Cardiac autonomic neuropathy (CAN) is a serious complication of diabetes mellitus that is strongly associated with increased risk of cardiovascular mortality. CAN manifests in a spectrum of things, ranging from resting tachycardia, fixed heart rate arrhythmias, intraoperative cardiovascular instability and orthostatic hypotension to development of "silent" myocardial ischemia, "silent" myocardial infarction.

Diabetic patients should be screened for CAN due to the possibility of reversal of cardiovascular denervation in the early stages of the disease. Cardiovascular reflex tests and Holter-derived time and frequency-domain measurements are frequently used for the diagnosis. Therapeutic approaches are promising and may hinder or reverse the progression of the CAN when initiated during the early stages.

Introduction

Diabetes mellitus (DM) is a global epidemic affecting at least 8.3% of the population and 371 million people worldwide with a significant proportion (50%) remaining undiagnosed. It is estimated that almost one of six people are currently at risk of developing diabetes-related complications [1–4].

The majority of patients with long-term course of DM [mainly type 2 diabetes mellitus (T2DM)] are diagnosed

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with coronary heart disease (CHD) due to coronary vessels arterial sclerotic disease. Often the course of CHD is complicated by combination of hypertension, specific kidney arterial involvement, and eyes and lower limbs affection. Metabolic alterations in the myocardium are combined with early coronary atherosclerosis. All these changes in the heart which occur out of prolonged duration of DM among middle age and elderly patients [coronary vessels affection, myocardium changes, diabetic cardiac autonomic neuropathy (CAN), and arterial sclerotic disease] are associated with the term "diabetic heart or diabetic cardiomyopathy" [5, 6].

Cardiac autonomic neuropathy among T2DM patients is characterized by lesion of nerve fibers in the sympathetic and parasympathetic divisions of the autonomic nervous system and is diagnosed unsatisfactorily and may be accompanied by severe orthostatic hypotension (OH), decreased tolerance to the physical loadings, and cause cardiac arrhythmias, ischemia of coronary vessels, *"silent" myocardial infarction (MI)*, "sudden" death syndrome [7–10].

Definition of CAN

Cardiovascular autonomic neuropathy is defined as the impairment of autonomic control of the cardiovascular system in the setting of diabetes after exclusion of other causes [11]. CAN is caused by damage to the autonomic nerve fibers that innervate the heart and blood vessels and leads to abnormalities in cardiovascular dynamics [12]. CAN is usually documented by using several cardiovascular autonomic reflex tests (CARTs) [13–15].

Epidemiology of CAN

CAN is a common chronic complication of type 1 diabetes mellitus (T1DM) and T2DM and is associated with higher morbidity and mortality level among patients with DM. The prevalence of confirmed CAN in unselected people with T1DM and T2DM is around 20%, but figures as high as 65% are reported with increasing age and diabetes duration. Because many studies were hospital based, referral bias cannot be excluded (classes II and III). Clinical correlates or risk markers for CAN are age, diabetes duration, poor glycemic control, microvascular complications (peripheral polyneuropathy, retinopathy, and nephropathy), hypertension, and dyslipoproteinemia (classes I and II). Established risk factors for CAN are glycemic control in T1DM (class I) and a combination of hypertension, dyslipoproteinemia (DLP), obesity, and glycemic control in T2DM (class II) [14, 15].

Screening for CAN should be performed in asymptomatic T2DM at diagnosis and T1DM after 5 years of disease, in particular those at greater risk for CAN due to a history of poor glycemic control [*hemoglobin* A_{1c} (HbA_{1c}) > 7%], or the presence of one major cardiovascular risk factor (among hypertension, DLP, and smoking), or the presence of macro- or microangiopathic complications (level B). CAN screening may be also required in asymptomatic patients for preoperative risk assessment before major surgical procedures (level C) [14–16].

Risk Factors for the Diabetic Cardiac Autonomic Neuropathy

Current data that differentiate CAN in T1DM and in T2DM in terms of risk factors and natural history are summarized in Table 57.1 [17].

Possible factors associated with high mortality and sudden death due to autonomic neuropathy are [5]:

- Silent myocardial ischemia/infarction.
- Cardiorespiratory arrest/increased perioperative and perintubation risk.
- Resting tachycardia.
- Ventricular arrhythmias/prolongation of the QT interval (QTi).
- Hypertension.
- Orthostatic hypotension.

Table 57.1 Cardiac autonomic neuropathy in type 1 and type 2 diabetes mellitus: differences in relation to risk factors and natural history [17]

Diabetes mellitus		
Risk factors	Type 1 diabetes mellitus	Type 2 diabetes mellitus
Age	+	+
Gender (female)	+	–
Obesity	–	+
Hyperinsulinemia	NA	+
Duration of DM	++	++
Smoking	+	+
HbA_{1c}	++	++
Hypertension	++	++
Retinopathy	++	+
Hypertriglyceridemia	+	+
Classical diabetic peripheral neuropathy	++	++
Microalbuminuria	++	++
Dyslipoproteinemia (>LDL and <HDL)	+	(+)
Prevalence at diagnosis of DM	7.7%	5%
Prevalence after 10 years	38%	65%
Prevalence (random)	25%	34%

++ strong association; + moderate association; – not found; (+) controversial; NA not applicable

- Flattening of the nocturnal reduction of blood pressure (BP) and heart rate ("non-dipper" phenomenon).
- Exaggerated BP responses with supine position and exercise.
- Abnormal diastolic/systolic left ventricular function.
- Poor exercise tolerance.
- Impaired cardiovascular responsiveness.
- Heat intolerance due to defective sympathetic thermoregulation.
- Susceptibility to foot ulcers and amputations due to arteriovenous shunting and sudomotor dysfunction.
- Hypoglycemia unawareness.
- Increased risk of severe hypoglycemia.
- Obstructive sleep apnea syndrome.

Pathogenesis of CAN

Diabetic CAN is eventually caused by complex interactions among a number of pathogenic pathways. Hyperglycemia is the leading cause of the initiation of this pathogenic process [12, 18–20]. The pathogenesis of diabetic CAN is multifactorial, including increased mitochondrial production of free radicals due to hyperglycemia-induced oxidative/nitrosative stress. Neuronal activity, mitochondrial function, membrane permeability, and endothelial function are impaired by advanced glycosylation end product formation, polyol aldose reductase signaling, protein kinase C and poly(ADP ribose) polymerase activation, and the alteration of the Na^+/K^+-ATPase pump function. Neuronal apoptotic processes are precipitated by endoplasmic reticulum stress induced by hyperglycemia, along with impaired nerve perfusion, DLP, alterations in redox status, low-grade inflammation, and disturbance in Ca^{2+} balance [21–24].

Classification of Diabetic Cardiac Autonomic Neuropathy [25]

Subclinical phase:

- Decreased heart rate variability.

Early phase:

- Resting tachycardia.

Advanced stage:

- Exercise intolerance.
- Cardiomyopathy with left ventricular dysfunction.
- Orthostatic hypotension.
- Silent myocardial ischemia.

Clinical Impact of CAN

Clinical Manifestations of CAN

Symptomatic manifestations of CAN include sinus tachycardia, exercise intolerance, and orthostatic hypotension. Orthostatic hypotension (OH) was present in 6–32% of diabetic patients depending on diagnostic cutoffs for fall in systolic blood pressure (20 or 30 mmHg) and the diabetic populations studied [15, 26, 27]. Symptoms of orthostatic intolerance were present in 4–18% of diabetic patients [14, 26, 27]. Orthostatic symptoms, such as light-headedness, dizziness, blurred vision, fainting, or pain in the neck or shoulder when standing, may be worse in the early morning, after meals, during a rise in core temperature, during prolonged standing, or with physical activity [28, 29]. Symptoms may be disabling, are often a barrier to an effective antihypertensive treatment, and may lead to falls in the elderly.

A number of other cardiovascular abnormalities were found in association with CAN [30]. These may play a role in excess mortality and morbidity and contribute to the burden associated with CAN (Table 57.2).

Symptoms and signs associated with diabetic CAN are presented in Table 57.3.

Table 57.2 Abnormalities associated with cardiovascular autonomic neuropathy at the level of cardiovascular system and peripheral vascular function [15]

Cardiovascular system	Peripheral vascular function
Perioperative unstability	↑ peripheral blood flow and warm skin
Resting tachycardia	↑ arteriovenous shunting and swollen veins
Loss of reflex heart rate variations	↑ venous pressure
Hypertension	Leg and foot edema
Exercise intolerance	Loss of protective cutaneous vasomotor reflexes
Orthostatic hypotension	Loss of venoarteriolar reflex with microvascular damage
Postprandial hypotension	↑ transcapillary leakage of macromolecules
Silent myocardial ischaemia	↑ medial arterial calcification
Left ventricular dysfunction and hypertrophy	–
QT interval prolongation	–
Impaired baroreflex sensitivity	–
Non-dipping, reverse dipping	–
Sympathovagal imbalance	–
Dysregulation of cerebral circulation	–
↓ sympathetically mediated vasodilation of coronary vessels	–
↑ arterial stiffness	–

Table 57.3 Symptoms and signs associated with diabetic cardiac autonomic neuropathy [20]

Diabetic cardiac autonomic neuropathy	
Resting tachycardia	
Abnormal blood pressure regulation	Nondipping Reverse dipping
Orthostatic hypotension (all with standing)	Light-headedness Weakness Faintness Visual impairment Syncope
Orthostatic tachycardia or bradycardia and chronotropic incompetence (all with standing)	Light-headedness Weakness Faintness Dizziness Visual impairment Syncope
Exercise intolerance	

Morbidity and Mortality in Cardiac Autonomic Neuropathy

CAN is a significant cause of morbidity and mortality associated with a high risk of cardiac arrhythmias and sudden death, possibly related to "silent" myocardial ischemia (SMI). Cardiovascular disease remains the main cause of excess mortality among patients with T1DM and T2DM. Reduced heart rate variability (HRV) as a marker of autonomic dysfunction has been shown to have dire consequences in terms of morbidity (e.g., progression of coronary atherosclerosis) and mortality independent of cardiovascular risk factors in various populations, including those with prediabetes and DM [12, 31]. In T1DM patients, there is a fourfold increase risk of death [31–33]. CAN is significantly associated with overall mortality [7, 12, 15], and in some but not all studies with morbidity, such as SMI, coronary artery disease (CAD), stroke, diabetic nephropathy progression, and perioperative morbidity. In the Detection of Ischemia in Asymptomatic Diabetic Subjects (DIAD) study, a diminished Valsalva heart rate (HR) ratio (a measure of CAN) was strongly associated with SMI, independent of more traditional risk factors including sex, age, hypertension, and smoking [14, 15, 34]. In the European Epidemiology and Prevention of Diabetes (EURODIAB) study, autonomic dysfunction was present in one-third of T1DM patients and was strongly associated with coexisting cardiovascular disease (CVD) after adjustment to age, HbA_{1c}, and duration of diabetes [12]. Results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial again confirmed the association of CAN and mortality. These investigators showed that the individuals in this trial with baseline CAN were 1.55–2.14 times as likely to die as individuals without CAN [35]. Furthermore, CAN in the presence of peripheral neuropathy was the highest predictor of CVD mortality. Indeed, combining indexes of autonomic dysfunction have been shown to be associated with the higher risk of mortality [7, 33]. There is also strong evidence, based on studies in patients with T1DM and patients with T2DM with a mean follow-up of 9.2 years, that QT interval (QTi) prolongation is an independent predictor of mortality for all-cause and cardiovascular deaths [7, 30, 33, 36]. Thus, CAN assessment can be used for cardiovascular risk stratification in patients with and without established CVD, as a marker for patients requiring more intensive monitoring during the perioperative period and other physiological stresses and as an indicator for more intensive pharmacotherapeutic and lifestyle management of comorbid conditions. There is definitive evidence for a predictive value of CAN on overall mortality (class I). There is some evidence of a predictive value of CAN on morbidity (class II). Orthostatic hypotension, when due to advanced CAN, is associated with an additional increase in mortality risk over that driven by HRV abnormalities (class III). Some cardiovascular abnormalities, closely linked to CAN, are associated with increased mortality: tachycardia (class II), QTi prolongation (class II), and non-dipping status (class III) [15, 37].

CAN is a risk marker of mortality (level A), as well as a risk marker and likely a risk factor for cardiovascular morbidity (level B), and possibly a progression promoter of diabetic nephropathy (level C). Orthostatic hypotension is associated with a worse prognosis than cardiovagal neuropathy (level C). QTi prolongation has prognostic value in diabetes (level B). Non-dipping status is associated with an adverse cardiovascular prognosis in diabetes (level C). Non-dipping status predicts the progression from micro- and macroalbuminuria to renal failure in T2DM (level C) [15].

CAN Assessment

Methods of CAN assessment in clinical practice include assessment of symptoms and signs, *cardiovascular reflex tests* based on HR and blood pressure (BP), and ambulatory blood pressure monitoring (ABPM).

Assessment of Symptoms

Questionnaires have been developed to investigate orthostatic symptoms and their severity in dysautonomic conditions, although they have not been specifically validated for CAN, and validated translations in different languages are lacking. In the Rochester Diabetic Neuropathy Study, the correlation between the autonomic symptoms and the autonomic deficits was weak in T1DM and absent in T2DM patients [28, 29, 38]. Orthostatic symptoms were poorly related to fall in systolic BP on standing. For their clinical impact, orthostatic symptoms should be looked for regularly together with other dysautonomic symptoms in diabetic patients [15].

Assessment of Signs

Resting tachycardia: While abnormalities in HRV are early findings of CAN, resting tachycardia and a fixed HR are characteristic late findings in diabetic patients with vagal impairment. Resting HR of 90–100 b.p.m. and occasional HR increments up to 130 b.p.m. occur. The highest resting HR have been found in patients with parasympathetic damage, occurring earlier in the course of CAN than sympathetic nerve dysfunction; in those with evidence for combined vagal and sympathetic involvement, the rate returns toward normal but remains elevated. A fixed HR that is unresponsive to moderate exercise, stress, or sleep indicates almost complete cardiac denervation. A blunted HR response to adenosine receptor agonists was described in both patients with DM and patients with metabolic syndrome and attributed to earlier stages of CAN [34, 39]. Higher resting HR (>78 b.p.m.) compared with lower resting HR (<58 b.p.m.) and a rise in HR with time have been shown to be powerful, independent risk predictors for all-cause and CVD mortality in several prospective cohorts [9]. The prognostic value of resting HR is a useful tool for cardiovascular risk stratification and as a therapeutic target in high-risk patients [12, 31, 40].

Exercise intolerance: In diabetic patients without evidence of heart disease, but with asymptomatic cardiac vagal neuropathy, exercise capacity and HR, BP, and cardiac stroke volume responses to exercise were diminished. A further decrease in exercise capacity and BP response was seen in patients with both vagal neuropathy and orthostatic hypotension. It is generally recommended that diabetic patients suspected to have CAN should be tested with a cardiac stress test before undertaking an exercise program. The severity of CAN correlated inversely with maximal HR increase during exercise, suggesting CAN contribution to diminished exercise tolerance [14, 15, 41].

Orthostatic hypotension: Orthostatic hypotension is defined as a fall in BP (i.e., > 20 mmHg or more stringent criteria is >30 mmHg for systolic or >10 mmHg for diastolic BP) in response to postural change, from supine to standing [30, 41]. In patients with diabetes, OH is usually a result of damage to the efferent sympathetic vasomotor fibers, particularly in the splanchnic vasculature [12, 28]. Patients with OH are typically represented with lightheadedness and presyncopal symptoms. Symptoms, such as dizziness, weakness, fatigue, visual blurring, and neck pain, also might be a result of orthostatic hypotension. Many patients, however, remain asymptomatic despite significant falls in BP. Orthostatic symptoms can also be misjudged as hypoglycemia and can be aggravated by a number of drugs, including vasodilators, diuretics, phenothiazines, and particularly tricyclic antidepressants and insulin [30, 31].

QTi prolongation QTi prolongation has been defined as a QTc (corrected QT for heart rate) ≥460 ms in women and ≥450 ms in men, although in most studies less strict criteria were used. The pathogenesis of QTi prolongation is multifactorial and includes imbalance in cardiac sympathetic innervation, intrinsic metabolic and electrolytic myocardial changes, left ventricular (LV) hypertrophy, and CAD, and genetic factors could lead to QTi prolongation [36, 42]. The day-night modulation of the QT/relative risk relation—on 24-h ECG recordings—was altered in CAN patients free of CAD, LV dysfunction, or hypertrophy, with a reversed day-night pattern and an increased nocturnal QT rate dependence. Reversible QTi prolongation may be induced by hyperinsulinemia in healthy subjects, by hyperglycemia, and by acute hypoglycemia in both healthy and diabetic subjects [36, 43]. In T1DM patients, prolonged QTc was shown to occur frequently during overnight hypoglycemia and was associated with cardiac rate/rhythm disturbances. These findings support an arrhythmic basis for the "dead in bed" syndrome and possibly a provocative role of hypoglycemia-induced sympathetic activation in cardiovascular events [14, 44]. In a meta-analysis of 17 studies including 4584 diabetic patients, QTc prolongation (>441 ms) was a specific (86%) albeit insensitive (28%) index of CAN [38].

Impaired HRV: The earliest clinical indicator of CAN is a decrease in HRV. Variability in the instantaneous beat-to-beat HR intervals is a function of sympathetic and parasympathetic activity that regulates the cardiac functional response to the body's level of metabolic activity. In normal individuals, the HR has a high degree of beat-to-beat variability and HRV fluctuates increasing with inspiration and decreasing with expiration. Initially, clinical relevance of HRV was identified through observations that fetal distress is preceded by alterations in beat-to-beat intervals before any appreciable change occurs in HR itself. The serious implications of abnormal HRV became apparent only in the late 1980s, when it was confirmed that HRV was a strong, independent predictor of mortality after acute myocardial infarction [24, 30, 45, 46]

Non-dipping and reverse dipping: At night, health subjects exhibit a predominance of vagal tone and decreased sympathetic tone, associated with reduction in nocturnal BP. In diabetic CAN this pattern is altered, resulting in sympathetic predominance during sleep and subsequent nocturnal hypertension. This is associated with a higher frequency of LV hypertrophy and both fatal and severe nonfatal cardiovascular events in diabetic CAN subjects [14, 24, 38].

Ambulatory blood pressure monitoring is a standard tool in hypertension research and management with regard to diagnostic, prognostic, and therapeutic issues [47]. It allows the assessment of the diurnal BP pattern, which is mainly regulated by sleep-awake changes in the autonomic cardiovascular function. ABPM may be used for research purposes to:

- Evaluate the circadian BP pattern and its abnormalities (e.g., non-dipping, nocturnal hypertension, extreme dipping, morning surge).
- Study its relationship with autonomic dysfunction, sleep disturbances, and kidney function.
- Assess the 24-h BP response to treatment.
- Evaluate the longer term prognostic implications of circadian BP abnormalities.

Non-dipping and reverse-dipping patterns were associated with CAN, which was the major determinant of the circadian variation in blood pressure. Several observations in both diabetic and nondiabetic patients linked non-dipping to a disruption of the circadian variation in sympathovagal activity, i.e., a diminished increase in vagal activity and a sympathetic predominance during the night. The day-night difference in systolic BP was a moderately accurate diagnostic tool for CAN and reverse dipping as a specific (95%)—albeit insensitive (25%)—marker of CAN [15, 38]. In clinical practice, ABPM in the general population is useful for diagnostic purposes and provides unique and additional information for risk stratification with regard to hypertension-related organ damage and cardiovascular events and for the extent of BP response to treatment [24, 38]. The European Society of Hypertension acknowledges that ABPM may improve predictions of cardiovascular risk in hypertensive patients and recommends that 24-h ABPM should be considered in the presence of either noticeable variability of office BP values or a marked discrepancy between office and home BP values and in case of resistance to drug treatment or suspected hypotensive episodes [24, 38]. Thus, in patients with CAN, ABPM may be particularly useful in detecting non-dipping or reverse-dipping conditions, daytime postural BP changes, and postprandial hypotension and in achieving BP control for the whole 24-h period. Conversely, in clinical practice, the presence of reverse dipping in ABPM may suggest the presence of CAN and thus requires CAN testing [15, 38].

"Silent" myocardial ischemia/cardiac denervation syndrome: The presence of both symptomatic and asymptomatic CAD is increased in diabetic patients, and subclinical neuropathy is an important cause of SMI in patients with diabetes. Five of the 12 studies showed a statistically significant increased frequency of SMI in those with CAN compared with those without CAN [15, 38, 48]. "Silent" ischemia in diabetic patients can either result from CAN, from autonomic dysfunction attributable to CAD itself, or from both. The mechanisms of painless myocardial ischemia are, however, complex and not fully understood. Altered pain thresholds, subthreshold by ischemia not sufficient to induce pain, and dysfunction of the afferent cardiac autonomic nerve fibers have all been suggested as possible mechanisms [12, 38]. Features of a MI in patients with CAN are silence, cough, nausea and vomiting, dyspnea, tiredness, and ECG changes. Reduced appreciation for ischemic pain can impair timely recognition of myocardial ischemia or infarction, thereby delaying appropriate therapy. Thus, patients with CAN warrant more careful attention, and cardiovascular autonomic function testing might be an important component in the risk assessment of diabetic patients with CAD [12].

Intraoperative cardiovascular liability Perioperative cardiovascular morbidity and mortality are increased two- to threefold in patients with diabetes. Compared with nondiabetic subjects, diabetic patients undergoing general anesthesia might experience a greater degree of decline in HR and BP during induction of anesthesia and less of an increase after tracheal intubation and extubation. Vasopressor support is required more often in diabetic individuals with CAN than in those without CAN [30, 49]. The normal autonomic response of vasoconstriction and tachycardia does not completely compensate for the vasodilating effects of anesthesia. There is an association between CAN and more severe intraoperative hypothermia that can result in decreased drug metabolism and impaired wound healing. Reduced hypoxic-induced ventilatory drive [30] requires preoperative CAN screening for loss of HRV. Preoperative cardiovascular autonomic screening might provide useful information for anesthesiologists planning the anesthetic management of diabetic patients and identify those at greater risk of intraoperative complications [12, 30].

Thus, resting HR is not a specific sign of CAN (class IV). After exclusion of other causes, OH suggests an advanced CAN that should be confirmed by CARTs (class I). Orthostatic hypotension (class III), QTi prolongation (class II), and reverse dipping on ABPM are specific but insensitive indices of CAN (class III) [12].

In terms of recommendations, it may be advised that the presence of symptoms and/or signs is not a sufficient criterion for CAN diagnosis but should provide the motivation to perform CAN testing to get a definite diagnosis (level B). Screening of orthostatic symptoms is advisable in any diabetic patient (level B). Regardless of the presence of orthostatic symptoms, the OH test is recommended yearly, in particular in patients over the age of 50 and in hypertensive diabetic patients (level B). CAN testing offers a useful tool to identify patients with potentially poor exercise performance and to prevent adverse outcomes when patients are introduced to exercise training programs (level C). Diabetic patients with unexplained tachycardia should undergo CAN testing (level C). Resting HR may be used in clinical practice for cardiovascular risk stratification (level C). QTi prolongation alone is an insufficient measure of CAN but should prompt further testing (level B). QTc may be used for cardiovascular risk stratification (level B).

ABPM should not be routinely employed for the diagnosis of CAN (level C). However, it is a reliable research tool

to explore 24-h BP patterns in different conditions (level B). In the presence of reverse dipping, referral for CAN testing is advisable (level C). ABPM may be useful in patients with CAN to detect non-dipping, to determine risk stratification for cardiovascular mortality and nephropathy progression, and to adjust antihypertensive treatment (level C) [12].

Cardiovascular Autonomic Reflex Tests

Autonomic balance involves complex interactions with several physiological mechanisms that act to maintain heart rate and BP within normal limits. Recent investigations have suggested that autonomic dysfunction (e.g., heightened activity of the sympathetic nervous system and suppressed activity of the parasympathetic nervous system) impairs the ability of the *autonomic nervous system* to regulate the cardiovascular system. Thus, autonomic imbalance might be a key component involved in both the etiology and the clinical course of CVD. What is also emerging is that one needs to distinguish the difference between autonomic imbalance and clear evidence of autonomic neuropathy. Autonomic imbalance produces a number of interesting and trying clinical situations, such as orthostatic tachycardia, orthostatic bradycardia, and OH, and can be responsible for predisposition to arrhythmias and "sudden" death [12, 40]. CARTs assess cardiovascular autonomic function through time-domain HR response to deep breathing, Valsalva maneuver, and postural change, and by measuring the end-organ response, that is, HR and BP changes, although indirect autonomic measures are considered the gold standard in autonomic testing. Heart rate variations during deep breathing, Valsalva maneuver, and lying-to-standing (HR tests) are indices mainly of parasympathetic function, whereas the OH, the BP response to a Valsalva maneuver, and sustained isometric muscular strain provide indices of sympathetic function. These tests are non-invasive, safe, clinically relevant (they correlate with tests of peripheral nervous system function), easy to carry out, sensitive, specific, reproducible, and standardized, and therefore they are considered consolidated, gold standard measures of autonomic function [12].

Diagnostic tests of CAN are summarized in Table 57.4.

Normal, borderline and abnormal values in tests of cardiovascular autonomic function are summarized in Table 57.5**.**

The Toronto Consensus [38] has concluded the following regarding diagnosis of CAN:

- The following CARTs are the gold standard for clinical autonomic testing: HR response to deep breathing, standing and Valsalva maneuver, and BP response to standing (class II evidence).
- These CARTs are sensitive, specific, reproducible, easy to carry out, safe, and standardized (classes II and III).
- The Valsalva maneuver is not advisable in the presence of proliferative retinopathy and when there is an increased risk of retinal hemorrhage (class IV).
- CARTs are subject to a number of confounding or interfering factors (class III).
- Age is the most relevant factor affecting HR tests (class I).
- A definite diagnosis of CAN and CAN staging requires more than one HR test and the OH test (class III).

The main clinical indications of the autonomic reflex tests are the following [15, 17, 38]:

- Diagnosis and staging of CAN in T2DM patients (at diagnosis and annually thereafter).

Table 57.4 Cardiovascular autonomic reflex tests [12]

Test	Technique	Normal response and values
Beat-to-beat HRV	With the patient at rest and supine, heart rate is monitored by ECG while the patient breathes in and out at six breaths per minute, paced by a metronome or similar device	A difference in HR of >15 beats per minute is normal and < 10 beats per minute is abnormal. The lowest normal value for the expiration-to-inspiration ratio of the R-R interval decreases with age: Age 20–24 years, 1.17; 25–29, 1.15; 30–34, 1.13; 35–39, 1.12; 40–44, 1.10; 45–49, 1.08; 50–54, 1.07; 55–59, 1.06; 60–64, 1.04; 65–69, 1.03; and 70–75, 1.02
Heart rate response to standing	During continuous ECG monitoring, the R-R interval is measured at beats 15 and 30 after standing	Normally, a tachycardia is followed by reflex bradycardia. The 30:15 ratio should be >1.03, borderline 1.01–1.03
Heart rate response to the Valsalva maneuver	The subject forcibly exhales into the mouthpiece of a manometer to 40 mmHg for 15 s during ECG monitoring	Healthy subjects develop tachycardia and peripheral vasoconstriction during strain and an overshoot bradycardia and rise in BP with release. The normal ratio of longest R-R to shortest R-R is >1.2, borderline 1.11–1.2
Systolic blood pressure response to standing	Systolic BP is measured in the supine subject. The patient stands, and the systolic BP is measured after 2 min	Normal response is a fall of <10 mmHg, borderline fall is a fall of 10–29 mmHg, and abnormal fall is a decrease of >30 mmHg
Diastolic blood pressure response to isometric exercise	The subject squeezes a handgrip dynamometer to establish a maximum. Grip is then squeezed at 30% maximum for 5 min	The normal response for diastolic BP is a rise of >16 mmHg in the other arm, borderline 11–15 mmHg

Table 57.5 Normal, borderline, and abnormal values in tests of cardiovascular autonomic function [5]

	Normal	Borderline	Abnormal
Tests reflecting mainly parasympathetic function			
Heart rate response to Valsalva maneuvre (Valsalva ratio)	≥1.21	1.11–1.20	≤1.10
Heart rate (R-R interval) variation	≥15 beats/min	11–14 beats/min	≤10 beats/min
During deep breathing (maximum-minimum heart rate) immediate heart rate response to standing (30:15 ratio)	≥1.04	1.01–1.03	≤1.00
Tests reflecting mainly sympathetic function			
Blood pressure response to standing (fall in systolic blood pressure in mmHg)	≤10	11–29	≥30
Blood pressure response to sustained handgrip (increase in diastolic blood pressure	≥16 mmHg	11–15 mmHg	≤10 mmHg

- Diagnosis and staging of CAN in T1DM patients (5 years after diagnosis and annually thereafter).
- Stratification of cardiovascular risk: in pre-operatory testing, pre-physical activity, indication of selective beta-blocker, and suspected silent ischemia.
- Differential diagnosis of other manifestations of CAN (regardless of DM duration): assess whether gastroparesis, erectile dysfunction, OH, dizziness, syncope, or tachycardia in diabetic persons are due to dysautonomia.
- Evaluate the progression of autonomic failure and monitor response to therapy (e.g., continuous infusion of insulin, post-transplants, and use of antioxidants).
- Differential diagnosis of other causes of neuropathy such as autoimmune autonomic neuropathy (chronic inflammatory demyelinating polyneuropathy, celiac disease, amyotrophy) or toxic-infectious neuropathy (alcohol, primary neuritic *Hansen's* disease, human immunodeficiency virus) as well as in cases where the presence of autonomic neuropathy is disproportionate to the sensorimotor neuropathy.

The most sensitive and specific diagnostic tests currently available to evaluate CAN in clinical research are (1) HRV, (2) baroreflex sensitivity (BRS), (3) muscle sympathetic nerve activity (MSNA), (4) plasma catecholamines, and (5) heart sympathetic imaging [50].

Heart Rate Variability

Heart rate is never completely stable. Continuous tonic, phasic, and transient external and internal stimuli of multiple origins affect HR to a variable but measurable extent. Five different mechanisms have been described: (1) sympathetic and parasympathetic efferences to the sinus node; (2) neurohumoral influences (e.g., catecholamines, thyroid hormones), (3) stretch of the sinus node, (4) changes in local temperature; and (5) ionic changes in the sinus node. Under resting conditions, it can be assumed that the short-term HRV is essentially determined by the first and third factors. The sympathetic and parasympathetic stimuli directly influence HR and are responsible for a physiologic variation in the heart rate, or HRV. The HRV can be evaluated in the time and frequency domains [38, 45, 50].

Time-domain measures of the normal R-R intervals include the difference between the longest and shortest R-R intervals, the standard deviation of 5-min average of normal R-R intervals (SDANN), and the root-mean-square of the difference of successive R-R intervals (rMSSD). Longer recordings (e.g., 24-h) allow the calculation of additional indices, as the number of instances per hour in which two consecutive R-R intervals differ by more than 50 ms over 24 h (pNN50). Essentially, all these indices explore the parasympathetic activity.

In the frequency domain, the use of spectral analysis of R-R interval (and other cardiovascular and respiratory signals) allows a precise description of the different fluctuations. The components of the HRV obtained by spectral analysis provide information about both the sympathetic and parasympathetic influences on the heart [38, 50]. Based on studies using acceptable techniques, there is evidence of reduced parasympathetic modulation of HR in diabetes and also reduced modulation of systolic BP in the low-frequency region [38, 51] particularly after sympathetic stimulation in response to tilting or in the microcirculation. As most of the CARTs essentially explore the parasympathetic activity, there is no other simple test of sympathetic activity capable of identifying early (functional or anatomic) autonomic sympathetic abnormality [50]. CARTs are considered the gold standard for CAN testing. Impaired HRV time- and frequency-domain indices have been reported in diabetic patients before CARTs abnormalities arise. However, the few studies that assessed the diagnostic accuracy against the reference standard of CARTs found only fair results. Time- and frequency-domain analysis of 24-h ECG recordings has documented an abnormal nocturnal sympathetic predominance in diabetic patients that was linked to BP non-dipping. In obese patients, weight loss was associated with an improvement in global HRV and in parasympathetic HRV indices [7, 50].

In this way, HRV testing is a clinically relevant measure in addition to CARTs and provides key information about autonomic-parasympathetic and sympathetic-modulation of the cardiovascular system. Analysis of HRV can be done using statistical indices in the time and frequency domains. Time-domain indices of global HRV and total spectral power of HRV represent the index of parasympathetic activity, as well as the HRV spectral power in the high-frequency region, while the relative proportion (not the absolute power) in the low frequencies of HRV provides a relative measure of sym-

pathetic modulation. This interpretation should be made with cautions if respiratory artifacts (slow breaths) cannot be excluded. Application of the technique is critically dependent upon understanding of the underlying physiology, the mathematical analyses used, and the many confounders and possible technical artifacts [46, 50].

In this way, misinterpretation of power spectrum takes place due to irregular respiratory pattern and verbalization during breathing, creating artifactual low frequencies and false "sympathetic overactivity."

Use of the absolute power of R-R interval low-frequency spectral data as evidence of sympathetic activity. In case of very low HRV (2–4% of total variability found in healthy subjects), the interpretation of spectral components is affected by the presence of non-autonomic components in the respiratory range. Other confounding factors (such as drugs) similar as those reported for CARTs [50, 52].

Recommendations [50]

- The best approach to HRV testing involves the analysis of ECG recordings in conjunction with respiration and beat-to-beat BP recordings (level C). When respiration cannot be recorded, breathing rate should be controlled (15 breaths/min) and hyperventilation or slow deep breathing avoided (level B). The subjects must not speak during recordings (level C). The optimal recording time is 4–5 min during well-controlled rest. Longer times (7 min) may be preferable if fast Fourier transform methods are used and if frequent ectopics are to be edited. Long uncontrolled recording times should be avoided (level C). When testing is done under stable conditions, autoregressive or fast Fourier transform methods can be used. When fast changes are to be expected (e.g., during interventions), autoregressive algorithms are preferred or alternatively special time-varying techniques.
- Age-related reference curve should be obtained for the healthy population in the same environment, and using the methodology adopted, construct 95% confidence limits (level B).
- Other recommendations on confounding factors are similar as those reported for CARTs.
- Used with the appropriate methodology, HRV has an increasingly important role in clinical research and therapeutic trials.

During 24-h Recordings

- If the goal is to define the circadian pattern of autonomic activity, long-duration spectra (e.g., 1 h) and autoregressive algorithms are preferable.
- If the goal is to define relatively faster modifications, shorter time windows (e.g., 5 min) are preferable. Special time-varying techniques can provide beat-to-beat autonomic changes.

Heart Rate Turbulence

Another Holter-based technique for evaluating CAN is the HR turbulence (HRT). HRT refers to sinus rhythm cycle length fluctuations following isolated premature ventricular beats. After an initial acceleration, the sinus rate decelerates after a premature ventricular beat. There are two components of HRT, turbulence onset and turbulence slope. A transient vagal inhibition triggers the mentioned initial acceleration in HR as a response to the missed baroreflex afferent input due to hemodynamically ineffective ventricular contraction. The successive deceleration in heart rate is caused by a sympathetically mediated overshoot of arterial pressure through vagal recruitment. HRT evaluation can be used in the risk assessment after acute MI and in the monitoring of disease progression in heart failure and CAN [22, 53]. A turbulence slope of below 3.32 ms/R-R is 97% sensitive and 71% specific for the diagnosis of CAN as detected by the CART in patients with T2DM [22, 54].

Baroreflex Sensitivity

The BRS is an interesting approach as it combines information derived from both HR and blood pressure. The measurement of the cardiac vagal arm BRS can be done with several methods: drugs or physical maneuvers can be applied to modify BP; alternatively, spontaneous blood pressure variations can be used. In all cases, the response in heart rate to the changes in BP is quantified. None of the BRS tests available today—based on drug-induced or physically induced changes in BP, spontaneous BP fluctuations with the sequences technique, or spectral analysis—have shown so far a definite advantage over the others or a clinically relevant difference [50, 55].

Longitudinal studies have demonstrated that BRS has important independent prognostic value in cardiac patients [50, 55] and in diabetic patients. Although some observations in diabetic patients support an early impairment of BRS before CARTs abnormalities, very few studies have evaluated so far the diagnostic accuracy of BRS measures as compared with the reference standard of CARTs with inconsistent results. Thus, no definite conclusion is possible on the diagnostic characteristics for CAN of BRS assessment, in particular on its sensitivity. In patients without CAN, an early stage of functional BRS abnormalities [17, 50] still responsive to lifestyle intervention—physical training or dietary improvement and weight reduction—has been documented.

BRS assessment may warrant use for identifying subjects at risk for CAN and also in clinical trials [50, 56].

In this way, cardiac vagal BRS assessment is an important component of autonomic testing as it combines information derived from both HR and blood pressure. Cardiac vagal BRS is a widely recognized independent prognostic index for cardiovascular mortality and morbidity in the general—mainly cardiac and the diabetic—population (class II). No definite conclusion is possible on the diagnostic characteristics of BRS assessment (classes III–IV). The presence of early abnormalities with respect to CARTs and their reversibility with appropriate treatments warrant the clinical use of BRS in identifying subjects at risk for CAN and to test potential therapeutic approaches (classes II–III). Pharmacological methods allow assessment of BRS across a range of physiologically relevant BP and when used with microneurography measurement of the sympathetic baroreflex. But this invasive technique is limited to research purposes. The methodology of BRS (in particular spontaneous BRS) is simple and fast. All BRS techniques require a dedicated beat-to-beat noninvasive blood pressure monitor. None of the BRS tests today available have shown a definite advantage over the other or a clinically relevant difference (class II) [50].

Fluctuations induced by drifts of the noninvasive blood pressure monitors. Most methods need a large number of arbitrary constraints imposed by the calculations that may affect the results. Respiratory pattern: although BRS measures in general do not need a strict control of respiratory pattern, slow breathing increases BRS and reduces sympathetic efferent drive; therefore, some feedback from respiration is necessary to correctly interpret the results. Age-related reduction in BRS. Other confounding factors (e.g., drugs) are similar as those for CARTs [50].

If the spontaneous approach is adopted, it is suggested to use a battery of methods based on the simplest single 5-min recording procedure (spontaneous BRS) and present the results in terms of a central measure (average or median) (level C) [50]:

- Recording should be performed during spontaneous breathing for 4–5 min, under monitored respiration or during controlled breathing at 15 breaths/min (level C).
- Pre-filtering of the data improves the agreement between methods and provides a more robust estimate of BRS (level C).
- The recording time should be kept between 4 and 5 min of well-controlled rest. Avoid long uncontrolled recording times (level C).
- The subjects must not speak during recordings (level C).
- Age-related reference curves should be obtained from the healthy population of the same environment and for the methodology adopted and construct 95% confidence limits (level B).
- Other recommendations on confounding factors are similar as those reported for CARTs.

Muscle Sympathetic Nerve Activity

Increased resting MSNA and blunted responsiveness to physiological hyperinsulinaemia or glucose ingestion have been described in T2DM having neuroadrenergic autonomic dysfunction and resembles insulin-resistant states and obesity. MSNA abnormalities in these conditions reverse with weight loss [50]. In contrast, T1DM is associated with a significant decrease in the number of bursts by about half [57]. Although reproducibility is similar to nondiabetic subjects, obtaining good-quality recordings is much more difficult in patients with diabetic polyneuropathy than in nondiabetic subjects [50], presumably as a result of a reduction in the conducting sympathetic nerve fibers.

In this way, the MSNA is the only method allowing direct and continuous measurement of sympathetic nerve traffic (class I). MSNA is the only method that can directly assess the sympathetic vascular arm of the arterial or cardiopulmonary baroreflex (class I). Type 1 diabetes appears to be associated with a reduction of MSNA (class IV). In early T2DM, resting MSNA might be increased, possibly due to hyperinsulinemia (class IV). The technique is difficult, invasive, and time-consuming, requires specialized trained operator, and cannot be repeated often in the same subject (class II) [50].

Confounders. BP variation, large inter-individual variations, food intake, age, posture, hypoxia, hydration, exercise, female reproductive hormones, arousal, sleep, mental stress, and ethnicity [50].

Recommendations. MSNA should not be routinely employed for the diagnosis of CAN (level C). MSNA should be employed with standard CARTs or for specific tests aimed at measuring vascular sympathetic modifications (e.g., glycemic clamps) (level C) [50].

Catecholamine Assessment and Cardiovascular Sympathetic Tests

Norepinephrine plasma appearance rate is in principle the biochemical equivalent of MSNA. Norepinephrine plasma appearance rate and clearance have been determined in idiopathic autonomic neuropathy as well as in diabetic CAN. While norepinephrine clearance is low in idiopathic autonomic neuropathy, this was not the case in CAN, and accordingly in diabetic CAN no additional diagnostic power was added by the inclusion of [^{3}H]-norepinephrine kinetic studies [50, 58]. Thus, catecholamine kinetics is an interesting technique which may give more information about catecholamine production and clearance across different regions but

is unsuitable to be used as a diagnostic tool yet. Plasma dihydroxyphenylalanine (DOPA) is not related to sympathetic neuropathy and has a mixed neuronal and non-neuronal origin. Plasma 3,4-dihydroxyphenylglycol (DHPG) may be a more sensitive marker of overall sympathetic innervation than supine plasma norepinephrine [50], and simultaneous measurement of norepinephrine and DHPG yields more information than measurement of either alone. Catecholamine assessment in diabetes showed in general lower than normal responses to postural changes, exercise, hypoglycemia, and CARTs. A subnormal orthostatic increment in plasma norepinephrine is a specific but not sensitive index of baroreflex-sympathoneural failure or sympathetic noradrenergic denervation [50].

Highlights. Clinical investigations including catecholamine determinations have contributed significantly to the understanding of the pathophysiology of CAN (class III). In the diagnostic context, the significance has been less prominent, partly due to the limited inclusion of the essays in clinical evaluations. Plasma catecholamine concentrations can indicate sympathetic noradrenergic and adrenomedullary hormonal system activity. Because levels of catecholamines are extremely responsive to lifestyle factors such as posture, temperature, dietary intake, medications, distress, and comorbidities, the clinical diagnostic value of plasma levels of catecholamines depends importantly on controlling or monitoring these factors (class III). Whole-body plasma norepinephrine and epinephrine respond rather slowly (minutes) to different physiological maneuvres. During turnover studies, different regional norepinephrine and epinephrine activities are "diluted" into a large plasma pool, contributing to blunted responses. Standardization of experimental conditions is to a large extent prohibitive for clinical routine purposes. In general, there is no neurochemical index that specifically assesses cardiac sympathetic innervation or function. This requires measurement of rates of entry of norepinephrine into the venous drainage of the heart, in turn requiring right heart catheterization, measurement of coronary sinus blood flow, and infusion of tracer-labeled norepinephrine [50]

Confounders. Plasma norepinephrine concentrations increase with age. Thus, age matching is mandatory for comparisons. Smoking increases sympathetic nervous activity and catecholamine concentrations; 24 h tobacco abstention is required for comparisons. Posture, emotional stress, and ambient temperature all affect catecholamine concentrations and should thus be standardized [50].

Recommendations. In a number of experimental conditions, plasma catecholamine measurements are mandatory. For clinical routine diagnosis and staging of CAN, the usefulness of plasma catecholamine concentrations is less obvious (level C). Plasma norepinephrine, epinephrine, and DHPG concentrations should be measured when whole-body sympathetic activity is assessed together with other relevant physiological parameters (HR, BP, cardiac output, hormonal and metabolic events) [50].

Heart Sympathetic Imaging and Heart Function Tests

Direct assessment of cardiac sympathetic innervation is possible using radiolabeled catecholamines or sympathomimetic amines that are actively taken up by sympathetic nerve terminals. Although in principle, it is possible to directly assess the integrity of both the parasympathetic as well as the sympathetic nervous system, there has been a paucity of research on parasympathetic imaging of the heart. Cardiac sympathetic neuroimaging, before and after administration of particular pharmacologic probes, can assess specific aspects of neuronal function. This combination has rarely been used [50].

Four tracers have been utilized to visualize the sympathetic nervous innervation of the heart: [^{123}I]-*meta*-iodobenzylguanidine (MIBG), [^{11}C]-*meta*-hydroxyephedrine (HED), 6-[^{18}F] dopamine, and [^{11}C]-epinephrine [32, 50, 59, 60].

The washout rates from the myocardium of [^{11}C]-epinephrine or 6-[^{18}F]-dopamine can give information on vesicular integrity. In subjects with T1DM and CAN, the washout rates of [^{11}C]-epinephrine parallels those of [^{11}C]-HED, suggesting regional differences in vesicular uptake or retention. Causes of defective tracer uptake or increased washout from the heart are a matter of current research [50, 61].

The interpretation of findings using sympathetic neurotransmitter analogues is complicated by the fact that alterations in sympathetic nervous system tone may also affect the retention of these tracers, and this fact is often not considered as an explanation for the clinical findings. In the isolated rat heart model, elevated norepinephrine concentrations in the perfusion increased neuronal HED clearance rates consistent with the concept that neuronal "recycling" of HED can be disrupted by increased synaptic norepinephrine levels. Alternatively at high norepinephrine concentrations, non-neuronal uptake of HED into myocardial cells and impaired retention may be an interfering factor [50].

Additionally, interpretation of early myocardial [^{123}I]-MIBG retention is complicated by increased body mass index and diastolic BP which have been reported to reduce myocardial MIBG uptake. Moreover, difficulties and delays in acquisition of utilizable images can complicate the interpretation of the measurement obtained. The delivery of tracers is critically influenced by myocardial perfusion, so myocardial retention of tracers should be performed with a quantitative analysis of myocardial blood flow. This can be

performed using positron emission tomography in order to derive a myocardial retention index [50, 62]. However, although regional perfusion deficiencies can be excluded using single-photon emission computed tomography, quantitative analysis of regional myocardial perfusion cannot be performed. Additionally, myocardial ischemia or damage is also known to result in cardiac denervation which may occur in the absence of alterations in CARTs [32, 63], whereas CAN is associated with impaired vasodilatory capacity in response to adenosine. Anoxic ischemia severely decreases the efficiency of vesicular sequestration and thus accelerates the loss of radioactivity, giving the false impression of denervation. Left ventricular dysfunction in DM has also been reported to reduce [^{123}I]-MIBG retention and increased washout rate [50].

Highlights. Scintigraphic tracers directly assess the structural integrity of the sympathetic nervous system supply to the heart (class III). [^{123}I]-MIBG scanning and single-photon emission computed tomography are widely used and available at most secondary care institutions; however, MIBG scanning is approved and reimbursed for evaluation of pheochromocytoma and so far not for evaluation of cardiac sympathetic innervation. Most data relate to the evaluation of cardiac sympathetic integrity; few studies evaluate the respiratory system. The relationships of deficits in tracer uptake/washout to sympathetic neuronal integrity and function are poorly understood: current tracers may not be the most optimum. Combined neuroimaging-pharmacologic approaches are required. Scintigraphic data correlates with HRV testing but have greater sensitivity to detect changes in sympathetic neuronal structure and/or function [50, 64] (class III). Scintigraphic data correlate with indices of myocardial perfusion and LV dysfunction in T1DM (class III). Limited studies demonstrate that decreased "uptake" and excessive "washout" of MIBG-derived radioactivity is an adverse prognostic finding in a spectrum of conditions including DM and that scintigraphic data are affected by the quality of glucose control (class III). Cost of scintigraphic studies is considerable [32, 50, 65]

Confounders. Parasympathetic tracers are not yet generally available. [^{11}C]-HED and 6-[^{18}F]-dopamine positron emission tomography have limited availability and are not reimbursed. Damage to the myocardium and LV dysfunction interferes with tracer uptake and washout independently of changes in CARTs. Regional myocardial [^{123}I]-MIBG "uptake" is semi-quantitative and not a clean index of neuronal uptake, which occurs extremely rapidly. [^{123}I]-MIBG retention is affected by body mass index, diastolic BP, and local factors which influence the tracer uptake and retention. Delivery of tracers is critically influenced by myocardial perfusion (myocardial retention of tracers should be performed with quantitative analysis of myocardial blood flow) [50].

The effects of the following on the kinetics of myocardial tracer retention are poorly understood: age (except for 6-[^{18}F]-dopamine), gender, glucose, insulin, DLP, hypertension, and vasoactive agents. Methodology for the assessment of sympathetic integrity is not standardized. Normative values have not been developed [50].

Recommendations [50]

- Scintigraphic studies should not be routinely employed for the diagnosis of CAN and should be utilized in concert with standard CARTs (level C).
- Scintigraphic studies are extremely valuable in the identification of sympathetic noradrenergic denervation as a mechanism of neurogenic orthostatic hypotension (level B).
- [^{123}I]-MIBG single-photon emission computed tomography offers semiquantitative assessment, and [^{11}C]-HED, 6-[^{18}F]-dopamine, and [^{11}C]-epinephrine positron emission tomography offer quantitative assessment of cardiac sympathetic integrity (level B).
- There is no standardized methodology for scintigraphic assessment of cardiac sympathetic integrity, and only limited data on the reproducibility exist (level C).
- Scintigraphic tracer uptake is affected by myocardial perfusion, and tracer retention is affected by available energy for the active neuronal and vesicular uptake transporters (level C).
- The results of scintigraphy should be compared with an appropriate control population (level C).
- Scintigraphic studies offer good sensitivity to detect sympathetic neuronal loss in the heart (level C).
- Scintigraphy is appropriate to explore the effects of sympathetic denervation on cardiac physiology, metabolism, and function (level C).
- Scintigraphy is useful as a marker of cardiac sympathetic denervation in cross-sectional and longitudinal research studies (level C).

Diagnostic Criteria for CAN

No unanimous criteria for diagnosis of CAN have been adapted to date. A single abnormal result among the two or three heart rate tests actually performed was considered a sufficient criterion for early CAN diagnosis. However, the presence of abnormalities in more than one test on several occasions was indicated as preferable for diagnosis [38, 66]. In addition, the presence of two or three abnormal results (two for borderline, three for definite) among the seven autonomic cardiovascular indices (including the five standard CARTs and other time and frequency domain indices of HRV) was recommended as a criterion for CAN diagnosis [67].

The Toronto Consensus established four reasons why the diagnosis of CAN is relevant to clinical practice [38]:

- For diagnosing and staging the different clinical forms of CAN: initial, definite, and advanced or severe.
- For the differential diagnosis of clinical manifestations (e.g., resting tachycardia, OH, and dyspnea upon exercise) and their respective treatment.
- For stratifying the degree of cardiovascular risk and the risk of other diabetic complications (nephropathy, retinopathy, and "silent" myocardial ischemia).
- To adapt the goal of glycated hemoglobin (HbA_{1c}) in each patient: for example, those with severe CAN should have a less aggressive glycemic control due to the risk of asymptomatic hypoglycemia in these patients, while patients with initial stages of CAN should have a more intensive glycemic control.

CARTs are the gold standard clinical tests for cardiovascular autonomic neuropathy [38]. Following the eighth International Symposium on Diabetic Neuropathy in 2010, criteria for diagnosis and staging of CAN are defined in the CAN Subcommittee of the Toronto Consensus Panel statement [23, 38, 68]. Accordingly, only one abnormal CARTs result is sufficient to diagnose possible or early CAN among the seven autonomic function analysis (five CARTs, time-domain and frequency-domain HRV tests), two or three abnormal tests indicate definite or confirmed CAN; and severe/advanced CAN can be indicated by concurrent orthostatic hypotension [23, 38, 68].

Staging of CAN

Ewing et al. proposed a classification based on "early involvement" (one abnormal result on HR test or two borderline results), "definite involvement" (two or more abnormal results on HR tests), and "severe involvement" (presence of OH) [26]. An "autonomic neuropathy score"—obtained by scoring the results of CARTs—has been used with the dual advantage of quantifying the progression of CAN and providing an overall quantitative result [38]. While an abnormal OH test, result generally occurs late in diabetes and subsequent to abnormalities in the HR tests; no chronological order or a markedly different prevalence of abnormalities among the HR tests has been found [38, 67]. Considering progression from an early to an advanced involvement, instead of from parasympathetic to sympathetic neuropathy, would appear to be the most appropriate approach to CAN staging, although OH may on rare occasions precede abnormalities in HR tests [26, 38]. The available information regarding the duration required to progress from an earlier to a later stage of CART impairment is scant, and it is not documented that a progression to OH and symptomatic forms invariably occur in all patients. The combination of CARTs with tests for sudomotor function may provide a more accurate diagnosis of diabetic autonomic neuropathy [38].

Conclusions [38]

- The following CARTs are the gold standard for clinical autonomic testing: HR response to deep breathing, standing, and Valsalva maneuver, and BP response to standing (class II).
- These CARTs are sensitive, specific, reproducible, easy to perform, safe, and standardized (classes II and III).
- The Valsalva maneuver is not advisable in the presence of proliferative retinopathy and when there is an increased risk of retinal hemorrhage (class IV).
- CARTs are subject to a number of confounding or interfering factors (class III). Age is the most relevant factor affecting heart rate tests (class I).
- A definite diagnosis of CAN and CAN staging requires more than one HR test and the OH test (class III).

Recommendations [38]

- Diagnosis of CAN is based on the use of CARTs for HR response to deep breathing, standing, Valsalva maneuver, and for BP response to standing (level A).
- For the diagnosis and monitoring of CAN, more than one HR test and the OH test are required (level B).
- Performance of CARTs should be standardized and the influence of confounding variables minimized (level A).
- Age-related normal ranges of HR tests are strictly required (level A).
- CAN diagnosis and staging: (1) the presence of one abnormal cardiovagal test result identifies the condition of possible or early CAN, to be confirmed over time; (2) at least two abnormal cardiovagal results are required for a definite or confirmed diagnosis of CAN; and (3) the presence of OH in addition to HR test abnormalities identifies severe or advanced CAN (level B).
- CARTs allow CAN staging from early to advanced involvement (level C).
- Progressive stages of CAN are associated with increasingly worse prognosis (level B).

Management of CAN

Clinical effectiveness of CAN diagnosis in clinical forms of CAN and the awareness of CAN for the therapeutic strategy in asymptomatic forms of CAN are presented in Fig. 57.1.

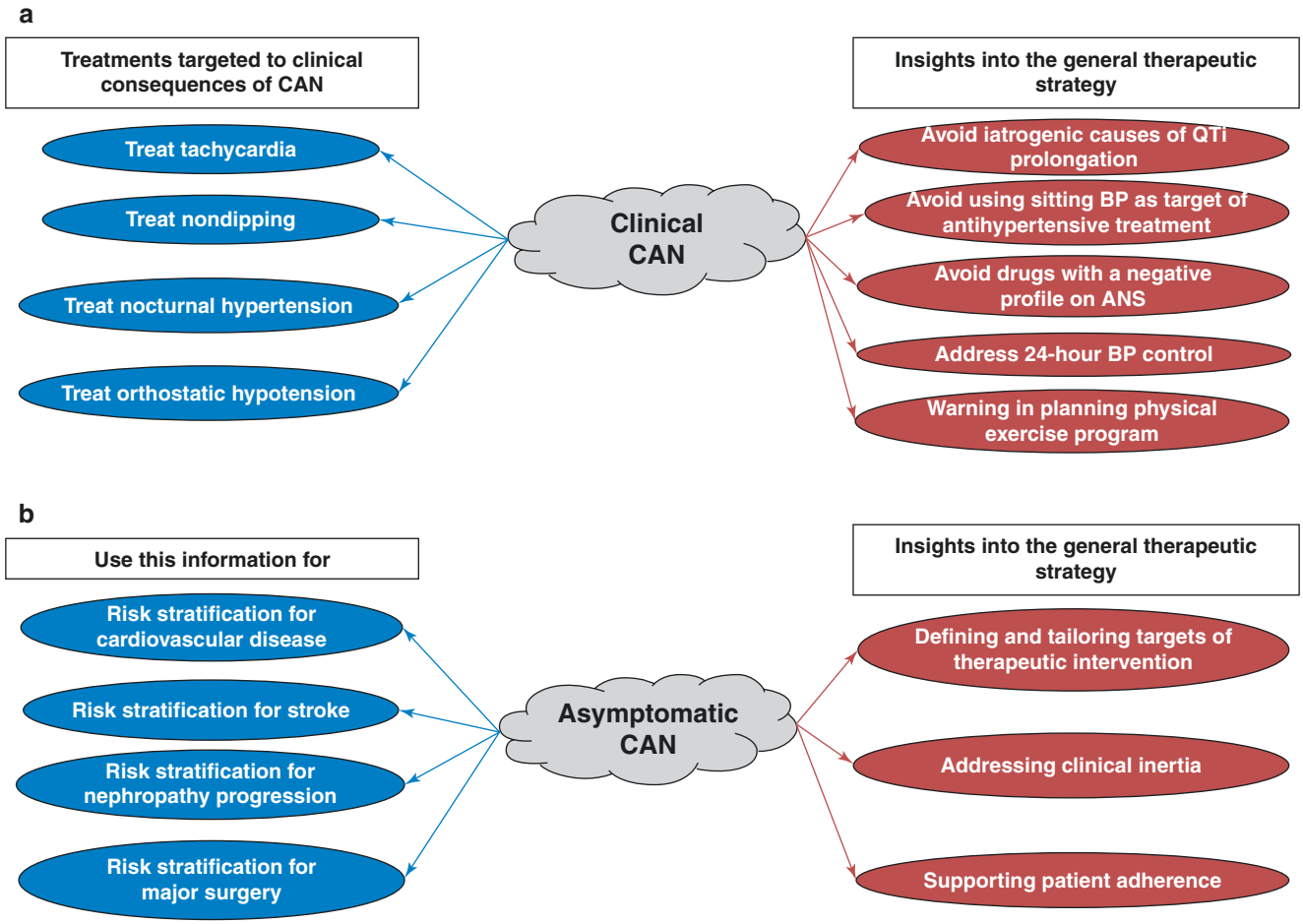

Fig. 57.1 (**a**) Clinical effectiveness of cardiac autonomic neuropathy (CAN) diagnosis in clinical forms of CAN and (**b**) the awareness of CAN for the therapeutic strategy in asymptomatic forms of CAN. *QTi* QT interval, *BP* blood pressure, *ANS* autonomic nervous system. (Adapted from Spallone V [14], with permission from Publisher. Copyright ©2019 Korean Diabetes Association From Diabetes Metab J. 2019 43:1:16. Reprinted with permission from The Korean Diabetes Association)

Intensive Glycemic Control and Multifactorial Risk Intervention

Compensation state of T2DM is recognized as a primary goal in the prevention of development and/or progression of CVD [2, 3, 18, 35, 69]. Insulin resistance (IR) is a defining feature in most cases of T2DM and plays a key role in the pathogenesis of myocardial alternations. Obviously, pharmacological agents that are used in the treatment of diabetes should have positive qualities for correction of functional and structural disorders of the cardiovascular system [10, 70]. Theoretically, pharmacological agents that improve insulin sensitivity [metformin, thiazolidinediones (TZD)] appear to be the most appropriate in this regard. It is established that metformin has a positive effect on glucose metabolism; Ca^{2+} concentration in cardiomyocytes, but metformin, unlike TZD, does not show any positive effect on optimization of glucose metabolism in the myocardium [6, 54]. TZD stimulates receptor transcription factors, activated by peroxisome proliferator-activated receptor-γ (PPAR-γ), which improves insulin sensitivity and reduces the level of circulating free fatty acids (FFA). It is likely that TZD, despite the absence of the myocardium PPAR-γ type receptors, improves the functional state of the myocardium by reducing the content of FFA. However, the use of TZD among patients with CVD is limited due to the possibility of fluid retention and/or development of edema [71].

In the Steno 2 study, an intensive multifactorial cardiovascular risk intervention reduced the progression or the development of CAN among T2DM patients with microalbuminuria [72]. However, the beneficial effect of intensive glycemic control on CAN in T2DM has not been specifically proven [14, 19, 73].

Lifestyle Modification

Nutrition and physical activity. Correction of obesity. Limit salt intake to 2–4 g/day. Limit smoking, alcohol, and foods that contain caffeine. It has been established that compliance with recommended lifestyle modifications (exercise, weight loss, etc.) helps improve insulin sensitivity level. Sedentary lifestyle (less than 1000 kcal/week) is accompanied by the risk of mortality three times higher than when living an active lifestyle. Dosed physical activity reduces hyperinsulinemia and encourages the tendency to normalize lipid metabolism in addition to body weight decrease. Physical activity is associated with higher HRV and lower HR, therefore may be a predictor of positive changes in HRV indices [46, 74]. Obtaining the necessary amount of energy combined with physiologic food ration forms the dietary principles. The traditional Mediterranean diet (Greece and Southern Italy) is associated with longevity and/or low mortality due to CVD complications, decrease incidence of T2DM, and low frequency of wide range of chronic diseases, including rheumatoid arthritis, Parkinson's disease, and others [25, 75, 76].

Treatment of Dyslipoproteinemia

For DLP pharmacotherapy using statins, fibrates, bile acid sequestrants, nicotinic acid and its derivatives, products of long-chain ω-3 and ω-6 polyunsaturated fatty acids (PUFA), or as an alternative, their combination with cholesterol absorption inhibitors [54, 77–79].

Statins Statins (along with lifestyle changes) should be prescribed to patients with T2DM aged over 40 where there is at least one of the risk factors for CVD (regardless of basic lipid levels); prescription of statins among patients with T2DM aged under 40 years without diagnosed CVD should be considered when low-density lipoprotein (LDL) cholesterol level exceeds 2.6 mmol/L [78, 80, 81]. Achievement of LDL level in the blood <1.8 mmol/L or reduction by 30–40% compared with initial level (in case of failure to achieve value targets in the course of the prescription of the maximum tolerable dose statin) is suitable for patients at high risk of CVD, particularly patients with T2DM. However, statins are often ineffective when used for treatment of atherogenic DLP as pharmacological agents to achieve reduction in triglycerides (TG) and increase high-density lipoprotein (HDL) cholesterol; statin use (even at high doses) only partially solves the problem of the risk of CVD [80, 82].

Fibrates Fibrates limit the availability of substrates for the synthesis of TG in the liver, encourage lipoprotein lipase effects, increase LDL receptor/ligand interaction, stimulate cholesterol secretion with bile, stimulate reverse cholesterol transport, that is accompanied by reduction of TG and very LDL (VLDL) cholesterol levels, and improve insulin sensitivity. Possible mechanisms that help fibrates improve insulin sensitivity are fibrate binding to receptors that activate PPAR-β enhances fatty acids oxidation in the liver and, consequently, causes increase of insulin sensitivity; fibrates are involved in the regulation of adipokine expression [adiponectin, leptin, tumor necrosis-α (TNF-α), resistin, etc.], accompanied by the increase of insulin sensitivity [83].

Bile acid sequestrants Bile acid sequestrants are safe lipid-lowering medicaments, however often causing gastrointestinal adverse reactions. The second-generation bile acid sequestrants, including colesevelam, bind bile acids with higher affinity and better tolerance. It is used as a supplement to diet therapy and physical activity to reduce the concentration of LDL cholesterol among patients with primary DLP, during monotherapy and/or in combination therapy with statins, and to improve glycemic control among patients with T2DM. In addition, it is important that the bile acid sequestrants reduce the concentration of glucose and HbA_{1c} in the blood (approximately 0.9%) [38, 84] and thus may be useful in the treatment of hypercholesterolemia among patients with T2DM.

Niacin Niacin is the most efficient pharmacological agent for raising HDL cholesterol level and, to a lesser extent, to reduce the concentration of TG and LDL cholesterol. It is reported that the therapeutic effect of prolonged forms of niacin on lipid profile occurs with the medicament intake in the dose range 0.5–2.0 g. A common reason for not using niacin, which significantly affects patient's susception and accurate application, is the problem of "flushing." Current approach to this issue is the use of combined prolonged form of niacin with laropiprant, an inhibitor of prostaglandin D_2 [77].

Long-chain ω-3 PUFAs The use of long-chain ω-3 PUFAs due to their effects on glucose homeostasis and IR (IR reduction in muscle > adipose tissue >> liver) presumably inhibits insulin secretion and delays the development of T2DM) influences the state of lipid metabolism (decrease TG concentrations, presumably increase the concentration of HDL, cholesterol, improve lipid profile among patients with T2DM and DLP), moderately reduces BP, improves endothelial function, reduces the inflammation, and improves antioxidant protection [79, 85–89].

Ezetimibe Ezetimibe is used as a nutrition and exercise supplement to reduce the concentration of LDL cholesterol, total cholesterol (TC), and treatment of homozygous familial hypercholesterolemia. Despite some reservations, ezetimibe remains the medicine of first choice among other pharmacological agents in the absence of target specific level of LDL cholesterol using statin monotherapy [81].

Combined treatment Therapy of first choice for T2DM in case of lipid profile correction is usage of statins to achieve

specific target of LDL cholesterol level <2.6 mmol/L for primary prevention and <1.8 mmol/L for secondary prevention of CVD. Failure to get this target is the indication to combine statins with other lipid-lowering agents of other pharmacological groups. A number of international guidelines as a compulsory component of CVD risk monitoring recommend to control apolipoprotein B level on the first-priority basis [81, 90].

Correction of Metabolic Abnormalities in the Myocardium

Correction of metabolic abnormalities in the myocardium is the basis of pharmacotherapy that aims at optimization of the energy metabolism of the myocardium. Pharmacological impact system includes the following main aspects: use of metabolism regulators; energy-saving solutions; activators of endogenic high-energy compounds and O_2 transportation; inhibitors of metabolic acidosis; membrane's protection (inhibition of lipid peroxidation membranes of cardiomyocytes); and stabilization of lysosomal membranes, neutralization of membranotropic action of humoral agents of lysosomal proteases, and others. Medicaments that enhance cell energy state (means of potential energy supply survival of ischemic myocardium). Deterioration of intracellular reserves of carbohydrates needs to be replenished by use of glycolysis activation measures. The use of macroergic phosphates (ATP, etc.) as a direct energy source is problematic, as the therapeutic effect of ATP in case of ischemia probably has less to do with disposing of its macroergic bonds but more with involving products of catabolism of ATP into energy metabolism of cardiomyocytes [6, 54].

Modulators of metabolism. Insulin resistance affects myocardial function by reducing glucose transportation and oxidation of carbohydrates, enhancing the use of free fatty acids, inhibition of Ca^{2+} transportation in the sarcolemma, violation of the structure, and function of regulatory contractile proteins of myofibrils. In case of DM, the reduction of myocardial energy formation leads to inhibition of glucose oxidation and preferential oxidation of fatty acids in the myocardium and skeletal muscle, which increases sensitivity to myocardial ischemia and leads to significant disturbances of Ca^{2+} homeostasis and deterioration of diastolic and systolic myocardial function. The presence of CAD among patients with diabetes worsens the disease and significantly increases cardiovascular mortality. It is considered that even the initial stages of glycemic profile violations may influence the myocardial metabolism and contribute to the development of cardiomyopathy [91]. It is important that myocardial dysfunction is a suppositive stage of chronic hyperglycemia elaboration. Thus, dysfunction of cells metabolism, rather than systemic hyperglycemia, is the reason for elaboration of cardiac malfunction [54, 76].

Metabolic medicaments. Optimization of myocardial energy metabolism is based on increased myocardial glucose oxidation, which enhances cardiac function and protects myocardial fibers from ischemic and reperfusion injuries. Myocardial use of glucose in case of chronic disease may be improved due to intake of the medicines that can improve fatty acids metabolism and inhibit their oxidation. New therapeutic approach has been implemented after advent of trimetazidine—the first representative of a new class of metabolic agents—inhibitors of 3-ketoacyl coenzyme A thiolase. *Trimetazidine* reduces oxidation of fatty acids; stimulates glucose intake; restores the link between glycolysis and carbohydrate oxidation, which leads to the formation of ATP, reducing O_2 consumption; redirects fatty acids toward phospholipids; and increases cell tolerance to ischemic and reperfusion injuries; increases the oxidation of glucose and the activity of Na^+, K^+-ATPase, and Ca^{2+}-pumps in the sarcoplasmic reticulum. Anti-ischemic properties of trimetazidine do not depend on changes in hemodynamics and are associated with a distinct recovery of mechanical function after ischemia, which makes it recognized as cardyo-cytoprotective agent. Trimetazidine prescription improves glucose metabolism, reduces endothelin-1 among patients with diabetic cardiomyopathy, is accompanied by a significant positive changes in ejection fraction parameters among patients with heart failure, and improves quality of life parameters and NYHA functional class [92]. Another pharmacological agent that facilitates the inhibition of metabolism of fatty acids is *perhexiline.* Perhexiline prescription to patients with heart failure significantly contributes to the improvement of EF, VO_2max, and quality of life. Unfortunately, the clinical use of this medicament is limited because of the risk of hepatotoxicity and peripheral neuropathy [93]. *Ranolazine* is the third antianginal pharmacological agent with a potential of metabolism modificator. However, the following factors do not allow to implement its use: the degree of inhibition of fatty acids metabolism is limited by physiological indicators; ranolazine prescription associates with the possibility of QTi interval prolongation [94].

Limitation of extracellular Ca^{2+} into the cell. Blockers of Ca^{2+}-channels show a protective effect on myocardium in case of ischemia. In terms of correction of cell power, the most pathogenetically efficient option is the use of Ca^{2+} blockers; however they only eliminate secondary dysfunction links of oxidative phosphorylation in mitochondria. Prescription of β-adrenergic receptor blockers for T2DM with CAD and CAN has significant pathogenetic grounds as high sympathetic activity that is followed by CAN, accelerates the development of CVD, and significantly affects prognosis. In addition, several studies demonstrated the ability of β-blockers to reduce the incidence of SMI episodes and improve prognosis among these patients. However, adrenergic receptors and β-blockers negatively affect the

performance of glycemic profile; increase the risk of hypoglycemia, showing a negative effect on blood lipid profile and can provoke acute heart failure. The above-described events occur with prescription of non-selective β-blockers. Selective β-adrenergic receptor blockers, including metoprolol, are free of side effects, including the effectiveness of metoprolol in the treatment of CVD demonstrated in numerous controlled studies. *Metoprolol* has cardioprotective properties; improves prognosis among patients with CAD; and has a fair tolerance in case of prolonged use. Cardioselective β-blockers can also balance the effects of autonomic dysfunction; in particular, by resisting sympathetic stimulation, they can restore parasympathetic–sympathetic balance. However, traditional antianginal agents that affect hemodynamic parameters (β-blockers, Ca^{2+} antagonists, etc.) have lower tolerance among elderly due to the high risk of the interaction of pharmacological agents with a significant incidence of side effects [6, 54].

Total HRV has been shown to be increased and parasympathetic/sympathetic balance improved by angiotensin-converting enzyme (ACE) inhibition in patients with mild autonomic neuropathy through increases in nerve blood flow [52, 66]. Prostaglandin analogs have been shown to be effective through the same mechanism [66, 74]. Cardioselective beta-blockers are considered to have positive effects on autonomic dysfunction. For example, the addition of metoprolol to ramipril therapy in patients with type 1 diabetes resulted in recovery of HRV parameters [11, 95]. Furthermore, bisoprolol improved HRV in heart failure [91]. In a study including individuals with long-term diabetes and diabetic neuropathy, the combination of ACE inhibition and angiotensin-receptor blockade improved autonomic neuropathy [12]. In addition, it was showed that losartan therapy significantly improved HRV in patients with ischemic cardiomyopathy [96]. Similarly, sympathovagal imbalance in heart failure patients was improved following the administration of spironolactone along with enalapril, furosemide, and digoxin [97]. Such evidence reveals that combination therapies appear to provide better results than monotherapies [22, 23].

Medicaments contain micro- and macro-elements, primarily Mg^{2+}. One of the risk factors that can decrease insulin sensitivity is hypomagnesaemia. It is suggested that Mg^{2+} deficiency plays a significant role in increasing the risk of diabetic macro- and microvascular complications and, especially, the risk of CAD [6, 76].

Thrombosis Prevention and Treatment

Platelets obtained from patients with T2DM and tested in vitro are characterized by a real ability to aggregate under the influence of ADP, adrenaline, collagen, arachidonic acid, and thrombin. Aggregation of platelets is significantly increased in the second, irreversible phase, which depends on the transformation of arachidonic acid into labile prostacyclin and thromboxane. Thus, the possibility of ADP receptors of platelet membranes blocking is a pathogenetically justified measure. Prescription of antiplatelet agents, namely acetylsalicylic acid (ASA), clopidogrel, and others, can help prevent blood clots, stenocardia, and development of MI. The active clopidogrel metabolite irreversibly binds to ADP receptor on the platelet membrane, which leads to inhibition of adenylate cyclase, inhibition of ADP-dependent secretion of platelet granules, and inhibition of ADP-dependent process of binding fibrinogen receptor to the platelet membrane, does not affect the expression of receptors directly, blocks myointymal proliferation in case of vascular damage, and unlike ASA does not affect the activity of cyclooxygenase. Effect of clopidogrel and ASA synergy is demonstrated in the study of platelet ex vivo. However, clopidogrel is a more effective pharmacological agent within the frames of the combined risk of MI, stroke, and the syndrome of "sudden death" reduction [54, 98].

Aldose Reductase Inhibitors

*Aldose reductase inhibitors (*ARI) inhibit the *polyol* pathway for *glucose metabolism*, preventing the reduction of the redox potentials. Analysis of the double-blind, placebo-controlled study established that tolrestat contributes to the improvement of independent tests results and vibration sensitivity among patients with symmetric diabetic peripheral neuropathy (DPN). *Zenarestat* prescription for 12 months was accompanied by a dose-dependent change in the spissitude of nerve tissue, increased the velocity of nerve impulses, and improved myocardial systolic function. *Zoporestat and ranirestat*—medicaments of a new generation of ARI group—showed sufficient efficacy in experimental studies [60].

While the use of aldose reductase inhibitors (epalrestat, fidarestat, and AS-3201), which reduce nerve sorbitol, had a positive influence on HRV in patients with mild abnormalities, they were ineffective in advanced CAN patients [54, 66].

Replacement Therapy with the Help of Myoinositol

Several individual clinical trials were conducted for the study of myoinositol efficacy in the treatment of diabetic neuropathy. The results are quite positive; but in the future, clinical double-blind, placebo-controlled trials are needed [99].

Aminoguanidine

Aminoguanidine improves capacity of nerve velocity, increases blood flow, inhibits the formation of advanced glycation end products, and delays the emergence and development of albuminuria. Analysis of controlled trials confirmed quite aminoguanidine high efficiency among patients with diabetic neuropathy, but the development of a number of side effects terminated their application. The use of aminoguanidine derivatives is accompanied by clinical efficacy and lack of adverse side effects [7, 73]. The results are promising, but need further clinical double-blind, placebo-controlled studies.

Neurotrophic Therapy

Inhibition of nerve growth factor (NGF) expression and its receptors suppresses NGF axonal retrograding transport and reduces the activity of small unmyelinated neurons and their neuropeptides, including substance P and gene-linked calcitonin peptide. The use of recombinant human NGF normalizes neuropeptide concentration and prevents the development of sensory neuropathy in the experiment. However, the results of clinical placebo-controlled studies deny the positive impact of recombinant human NGF among patients with diabetic neuropathy [7, 73].

Antineural Autoimmunity Human Immunoglobulin for Intravenous Use

Intravenous human immunoglobulin prescription is recommended for patients with diabetic peripheral neuropathy (DPN), which have signs of antineural autoimmunity symptomes. The side effects include headache, and the main danger could be the development of an anaphylactic reaction; however, it affects mainly patients with deficiency of immunoglobulin A [7, 73].

Endoneural Perfusion Inhibition with the Development of Hypoxia

Experimental and clinical studies have shown benefit in the efficiency of vasodilators when used for improvement of nerve flow velocity, but there is not enough information about the impact of vasodilators on the course of DPN during clinical double-blind placebo-controlled studies. The research results of characteristics that impact the angiotensin-converting enzyme inhibitors on heart rate variability parameters among diabetic patients with CAN appeared to show diametrically opposed results. In particular, prescription of *quinapril* for 3 months was accompanied by statistically significant increased parasympathetic activity, and the use of trandolapril for 12 months did not affect the performance of autonomic myocardial function. However, most of these pharmacological agents have no proven clinical and electrophysiological positive effects and have certain limitations and contraindications [30, 73].

Activation of Free Radical Stress

Considering that one of the major pathogenetic mechanisms of neuropathy is oxidative stress, the need for antioxidants prescription is obvious [100, 101]. Great therapeutic potential is observed in α-lipoic acid (α-LA) and creates pathogenic evidence for the use of this pharmacological agent [100, 101]. Mechanism of α-LA action is not fully developed, but specific attention should be paid to two hypotheses. First, α-LA phenomenon causes dose-dependent proliferation of neuroblastoma cultured cells. Changes in the membrane fluidity that are mediated through sulfhydryl groups α-LA are considered to cause this effect. This is confirmed by the following results of several studies, including experimental neuropathy induced by acrylamide, followed by a significant inhibition of proliferation of the above phenomenon; overlay and/or progression of experimental distal neuropathy, mainly caused by a decrease of content of substances in axons containing sulfhydryl groups (e.g., glutathione); α-LA in vivo and in vitro enhances spontaneous processes of expansion and improvement of the structural and functional nerve terminals membranes state; and prescription of α-LA stimulates the regeneration of nerve terminals in case of the partial denervation, as well as experimental hexacarbon neuropathy. Second, and the most probable mechanism, is the ability of α-LA to function as a radical binder (cleaner) [54, 67, 102].

Vitamins with Antioxidant Properties [a Liposoluble Vitamin B_1 (Benfotiamine)], Combined Medications

There are enough experimental and clinical results of studies that suggest that the hyperinsulinemia, IR, and chronic hyperglycemia in T2DM have a negative impact on the metabolism of thiamine particularly due to the inhibition of the functional state of the thiamine transporter-1 and thiamine transporter-2, responsible for the reabsorption of vitamin in the proximal tubules of the kidneys; and transketolase (TK) activity, which can lead to the congestion of intermediates in the initial stages of glycolysis [glyceraldehyde-3-phosphate (GA3P), fructose-6-phosphate (F6P), and dihydroxyacetone-phosphate]. Congestion of intermediates in case of chronic hyperglycemia increases the production of

free radicals in the mitochondria, followed by inhibition of glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Increased concentrations of GA3P, F6P, and GAPDH can initiate induced hyperglycemia, metabolic fates that favor the overlay of vascular injury, including activation of proteinkinase-C, accumulation of advanced glycation end products (AGEs), hexosamine biosynthetic fates activation, and dicarbonyl compounds. Activation with dicarbonyl compounds is followed by further stimulation of the AGEs formation, which is also associated with functional impaired and structural state of cardiomyocytes [59, 103, 104].

It is clear that the correction of thiamin deficiency must be performed using exogenous vitamin B_1 or benfotiamine (monophosphate S-benzoyl-thiamine, high-bioavailable liposoluble vitamin B_1 derivatives). Results of experimental and clinical studies suggest a positive effect of benfotiamine prescription on prevention of diabetic vascular disease progression. Benfotiamine broad therapeutic potential has a good efficiency on medications containing soluble thiamine derivatives for the purpose of regulating the activity of free radical processes, correction of endothelial dysfunction in case of CVD, and stabilization of clinical and antioxidant effects [105].

Benfotiamine can promote neuronal and vascular deficiency correction through the participation of nitrogen oxide processes, which have a significant therapeutic potential for the treatment of CVD. The use of thiamine and α-LA combination has a great significance in the treatment of diabetic angio-neuropathy. In particular, it demonstrated that prescription of benfotiamine and α-LA to patients with T1DM was followed by normalization of hyperglycemia and for 4 weeks it promoted the normalization of prostacyclin synthase suppressed by diabetes and increase of TK activity in monocytes in two to three times [105–107].

Fatty Acids Metabolism Disorders (γ-Linolenic Acid, Acetyl L-Carnitine)

Vasoactive prostanoids, metabolites and dihomo-γ-linolenic acid (DGLA), including prostaglandins and other eicosanoids, are necessary for the physiological behavior of nerve conductivity and blood flow. The results of double-blind, placebo-controlled studies showed that prescription of DGLA to patients with DPN is followed by positive dynamics in clinical course, as well as increase in the speed of nerve conductivity. L-carnitine's main function is to strengthen the metabolism of fatty acids, but there is experimental evidence of L-carnitine's ability to activate glucose metabolism. It is believed that T2DM is characterized by malfunction of L-carnitine exchange in the mitochondria. The results of several studies showed that prescription of L-carnitine helps to improve energy supplies and LV function. It is established that propionyl-L-carnitine improves the functional status, used as glucose energy oxidation in the rat's affected myocardium (despite the increased level of fatty acids). Nutrition of diabetic mice with obesity with L-carnitine addition increases the level of acyl-carnitine in the blood, muscle, liver, and adipose tissue and increases levels of pyruvate dehydrogenase activity in the muscles; prescription of zinc–carnitine mixture reduces hyperglycemia and improves glucose tolerance. L-carnitine infusion with the help of hyperinsulinemic-euglycemic clamp improves glucose profile control and reduces the concentration of circulating lipids. L-carnitine prescription for 3 or 6 months for newly diagnosed patients with T2DM with lipid metabolism disorders is followed by a statistically significant decrease in lipoprotein(a) [Lp(a)] levels. The results of double-blind, placebo-controlled studies among patients with verified hyperLP(a) established that L-carnitine (2 g/day) encouraged a significant decrease in the concentration of Lp(a) levels; L-carnitine incorporation into nutrition of patients with newly diagnosed T2DM is followed by similar changes; and combined L-carnitine with simvastatin (20 mg/day) treatment is much more efficient in decreasing the concentration of lipids, including TG and Lp(a) than statin monotherapy. Thus, L-carnitine can be used as one of the components for lipid-modifying therapy among patients with T2DM [108, 109].

ω-3 PUFAs Medications

A fundamentally new approach to assessing the biological role of eicosapentaenoic (EPA) and docosahexaenoic acid (DHA) is associated with long-term epidemiological studies results among Inuits, which established a small percentage of CVD. The Greenlandic Inuits were observed to have an increased bleeding duration, lower levels of TC, TG, and VLDL-cholesterol; and a significant increase in TC lipid membranes of EPA and DHA contents, arachidonic acid concentration reduction, and linoleic acid. For the first time, these results allowed to express a reasonable assumption about the protective effect of DHA and especially EPA from the damaging effects on the internal vessel wall capable of inducing experiment CAD—a phenomenon of TC activation—and high blood viscosity, enhanced the cyclic endoperoxide synthase, including prostaglandin H_2, thromboxane A_2 (TXA_2) activation of endothelial cell proliferation, hypercholesterolemia, and hypertriglyceridemia. Prescription of EPA and DHA is followed by a decrease in the "rigidity" of red blood cells, which is obviously associated with labilization of erythrocyte plasmalemma based on rapid and intensive incorporation of long-chain ω-3 PUFAs phospholipids into membrane and decreased synthesis of vasoconstrictor active ingredients [79].

The ability of exogenous EPA and DHA to incorporate phospholipid blood cell membranes and membrane phospholipids of endothelial cells blood vessels affects the fundamental plasmalemma properties and receptor function for the perception and processing of extracellular information. Accumulating long-chain polyenes acids labilizes plasmalemma, changing the microviscosity of its lipid matrix, which causes the transformation of the basic plasmalemma properties: permeability, generation of biopotentials, and ions transit. Changes in the lipid environment of receptor structures affects their functional activity and enzyme systems control in the cell, which primarily relates to the corpuscular adenylate cyclase, whose function is related to the metabolism of phospholipids [87, 110].

Analysis of experimental and clinical studies proves that ω-3 PUFA inhibit the absorption of cholesterol in the intestine and its synthesis in the liver, lead to increased clearance of lipoproteins in the blood, prevent the development of IR in experimental diabetes, decrease level of BP, dose-dependently prevent the development of diabetes, improve the sensitivity of platelets to ADP and collagen, contribute to positive changes in the parameters of coagulation and endothelial cells migration, and inhibit the proliferation of smooth muscle cells. However, the studies aimed to investigate the features of ω-3 PUFA in T2DM are numerically small, and obtained results do not always testify to their effectiveness [88, 89, 111]. In particular, the results of the ORIGIN trial demonstrated that administration of 1 g ω-3 PUFAs did not reduce the rate of death caused by cardiovascular reasons or their outcomes during a period of 6 years among patients with dysglycemia and additional cardiovascular risk factors. In this trial, the dose of ω-3 PUFA was not chosen on the basis of any estimate of its effect on TG levels; nevertheless, a significant reduction in the TG level was shown. However, this study did not apply to treatment of CAN, and it was decided to continue the study for a few more years [85]. In the same time, American Diabetes Association (ADA, 2005) recommended the prescription of α-LA and ω-3 PUFAs in algorithms of DPN treatment [66] and in ADA recommendations (2014) and results of some trials: prescription of ω-3 PUFAs in DLP treatment among patients with T2DM and cardiovascular diseases [1, 88].

Symptomatic Treatment of Orthostatic Hypotension

Orthostatic hypotension syndrome is manifested by dizziness and possibility of loss of consciousness. Hypovolemia and sympathoadrenal disorders are the most common characteristic features among patients with DM and orthostatic hypotension. Orthostatic hypotension among most diabetic patients progresses asymptomatically and, therefore, does not require correction. However, in severe cases, it is key traumatic factor [38, 112].

Treatment of OH is required only when symptomatic with the therapeutic goal to minimize postural symptoms rather than to restore normotension. The first step encompasses non-pharmacological measures with the attempt to (1) identify other causes of OH, e.g., volume depletion, and avoid, when possible, drugs exacerbating postural symptoms, such as psychotropic drugs, diuretics, and α-adrenoreceptor antagonists; (2) educate patients regarding behavioral strategies such as gradual staged movements with postural change, mild isotonic exercise, head-up bed position during sleep, physical counter-maneuvres (e.g., leg-crossing, stooping, squatting, and tensing muscles), use of portable folding chairs, increased fluid and salt intake if not contraindicated, drinking water rapidly, and avoidance of large meals rich in carbohydrates; and (3) use of elastic garment over the legs and abdomen. If symptoms persist despite these measures, a pharmacological treatment should be considered [38].

Treatment of symptomatic postural hypotension among patients with CAN is very complicated because of the need to achieve a balance between changes in BP in the vertical and horizontal position. The increase of peripheral venous inflow is achieved through the use of elastic tightening body linen. It is inappropriate to prescribe psychotropic and diuretic drugs and eliminate the possibility of electrolyte disorders and/or reduce the fluid volume [38].

The peripheral selective α_1-adrenergic agonist *midodrine* is a first-line drug that exerts a pressor effect through both arteriolar constriction and venoconstriction of the capacitance vessels. The dosing should be individually tailored (up to two to four times 10 mg/day, with the first dose taken before arising and use avoided several hours before planned recumbency particularly in patients with documented supine hypertension). Adverse events are pilomotor reactions, pruritus, supine hypertension, bradycardia, gastrointestinal symptoms, and urinary retention. *Midodrine* is the only medication approved by the Food and Drug Administration for the treatment of symptomatic orthostatic hypotension [38].

The *9-α-fluorohydrocortisone* is first-choice drug that acts through sodium retention, a direct constricting effect on partially denervated vessels, and an increase in the water content of the vessel wall leading to a reduced distensibility. Possible adverse effects include supine hypertension, hypokalemia, congestive heart failure, and peripheral edema. The initial dose should be 0.05–0.1 mg daily with individual titration to 0.1–0.3 mg daily [38, 112].

Erythropoietin was proposed to increase standing blood pressure via several mechanisms: (1) increasing red cell mass and central blood volume, (2) correcting the anemia frequently associated with severe CAN, and (3) neurohumoral effects on the vascular wall and vascular tone regulation. It can be administered in diabetic patients with hemoglobin levels under 11 g/dL subcutaneously or intravenously at doses between 25 and 75 U/kg three times/week with an hemoglobin target of 12 g/dL followed by lower maintenance doses [38, 112].

Other possible treatments include (1) *desmopressin acetate*, a vasopressin analogue useful to correct nocturnal polyuria and morning orthostatic hypotension; (2) *somatostatin analogues* aimed at inhibiting the release of vasoactive gastrointestinal peptides, enhancing cardiac output, and increasing forearm and splanchnic vascular resistance, with severe cases of hypertension as possible adverse events in diabetic patients; (3) *caffeine* and (4) *acarbose*, both useful in attenuating postprandial hypotension in autonomic failure [38, 112, 113].

While pharmacological treatments, such as midodrine, clonidine, octreotide, fludrocortisone acetate, erythropoietin, nonselective beta-blockers and pyridostigmine bromide appear promising, all have mild to severe side effects, including hypertension [22, 35].

New Glucose-Lowering Medications and Autonomic Nervous System

Sodium Glucose Transporter 2 Inhibitors (SGLT2i)

It would be of interest to understand whether some of the positive effects on the cardiovascular system of these drugs are mediated by interaction with the autonomic nervous system in the kidney or directly in the central nervous system. However, clinical trials with SGLT2i using ABPM do not confirm to a preferential lowering effect on nocturnal versus daytime systolic BP, despite the diuretic and natriuretic effect of these drugs and the dipping restoration found with SGLT2i in rat models of obesity and metabolic syndrome [14, 114].

Glucagon-like Peptide 1 Receptor Agonists (GLP1-RA)

Experimental findings in mice and rats document that the central and peripheral administration of a glucagon-like peptide 1 receptor agonist (GLP1-RA) increased heart rate, reduced frequency-domain indices of HRV, and increased sympathetic activity [14, 115].

However, it should be noted that the GLP1-RA effects on heart rate and the autonomic nervous system need to be reconciled with the favorable cardiovascular outcomes in clinical trials of at least some GLP1-RAs (liraglutide, semaglutide, exenatide ER) [14].

The Toronto Consensus Panel on Diabetic Neuropathy concluded the following in relation to CAN treatment [38]:

- Intensive diabetes therapy retards the development of CAN in T1DM (level A).
- Intensive multifactorial cardiovascular risk intervention retards the development and progression of CAN in T2DM (level B).
- Lifestyle intervention might improve HRV in prediabetes (level B) and diabetes (level B).
- Symptomatic orthostatic hypotension might be improved by non-pharmacological measures (level B) and by midodrine (level A) and/or fludrocortisone (level B).

The recommendations from the Toronto Consensus Panel on Diabetic Neuropathy are as follows:

Diabetes therapy in patients with type 1 and type 2 diabetes should consider the individual risk profile and comorbidities (class I).

Lifestyle intervention should be offered as a basic preventive measure (class I).

Given the limited evidence from very few large-scale randomized clinical trials, recommendations cannot be given for pharmacological and non-pharmacological treatments of CAN.

Drugs that might reduce HRV should be avoided in patients with CAN (class III).

Resting tachycardia associated with CAN can be treated with cardioselective beta-blockers (class I).

The first therapeutic approach in symptomatic orthostatic hypotension should consider the exclusion of drugs exacerbating orthostatic hypotension, correction of volume depletion (class I), and other non-pharmacological measures (class IIa).

Pharmacotherapy of symptomatic orthostatic hypotension should include midodrine (class I) or fludrocortisones or a combination of both in non responders to monotherapy (class IIa).

Because of the limited evidence, the potential risk of any pharmacological treatment should be thoroughly weighed against its possible benefit (class I).

CARTs should be used as end points in prospective observational and clinical trials.

Concluding Remarks

Cardiac autonomic neuropathy is a serious complication of diabetes mellitus that is strongly associated with increased risk of cardiovascular mortality.

Screening for CAN must be performed to asymptomatic patients with type 2 diabetes at diagnosis and type 1 diabetic patients after 5 years of disease, in particular those (but not only) at greater risk for CAN.

Diagnosis of CAN is based on the use of CARTs, which are considered as the gold standard for clinical autonomic testing: the presence of one abnormal cardiovagal test result identifies the condition of possible or early CAN, to be confirmed over time; (2) at least two abnormal cardiovagal results are required for a definite or confirmed diagnosis of CAN; and (3) the presence of OH in addition to HR test abnormalities identifies severe or advanced CAN.

Lifestyle intervention is a basic preventive measure and may improve HRV. Intensive diabetes therapy retards the development of CAN in type 1 diabetes and intensive multifactorial cardiovascular risk intervention retards the development and progression of CAN in type 2 diabetes. Resting tachycardia by CAN can be treated with cardioselective β-blockers. Pharmacotherapy of symptomatic orthostatic hypotension should include midodrine or fludrocortisone or a combination of both in nonresponders to monotherapy.

The promising methods include research and use of tools that increase blood flow through the vasa vasorum, including butaprost (prostacyclin analogue), TXA_2 blockers, and drugs that contribute into strengthening and/or normalization of Na^+, K^+-ATPase (cilostazol, a potential phosphodiesterase inhibitor), α-LA, DGLA, and ω-3 PUFAs and the simultaneous prescription of α-LA, ω-3 PUFAs, and DGLA [8, 20, 30, 67, 95]. In addition, the combination of α-LA, ω-3 PUFAs, DGLA, and ARI is the most rational pathogenetically justified use.

Multiple Choice Questions

1. At what timepoint screening for CAN must be performed?
   (a) Asymptomatic patients with T2DM at diagnosis and patient with T1DM after 5 years of disease.
   (b) Asymptomatic patients with T2DM after 5 years of disease and type 1 diabetic patients at diagnosis.
   (c) Only patients with clinical signs of CAN.
   (d) Only patients with the history of poor glycemic control.
   (e) Screening for CAN shouldn't be performed.
2. Which risk factors are known for the development of CAN?
   (a) Diabetes duration.
   (b) Poor glycemic control.
   (c) Microvascular complications.
   (d) Combination of hypertension, dyslipidemia and obesity.
   (e) All listed above.
3. What method is considered as a gold standard for CAN diagnosis?
   (a) CARTs.
   (b) Orthostatic hypotension.
   (c) QTc prolongation on ECG.
   (d) Reverse dipping on ABPM.
   (e) Resting tachycardia by physical assessment.
4. What result based on the use of CARTs could confirm definite CAN?
   (a) At least two abnormal results of cardiovascular tests/or two for borderline, and three for definite.
   (b) At least three abnormal results of cardiovascular tests/or three for borderline, and four for definite.
   (c) At least one abnormal result of cardiovascular tests/or two for borderline.
   (d) At least four abnormal results of cardiovascular tests.
   (e) Orthostatic hypotension.
5. What signs are needed to undergo CAN testing?
   (a) Orthostatic hypotension.
   (b) Resting tachycardia.
   (c) QTc prolongation.
   (d) Reverse dipping by ABPMA.
   (e) All of above.
6. List a definition that is true for CAN management and prevention.
   (a) Lifestyle intervention is a basic preventive measure.
   (b) Resting tachycardia can be treated with cardioselective β-blockers.
   (c) Intensive diabetes therapy retards the development of CAN in type 1 diabetes mellitus, and intensive multifactorial cardiovascular risk intervention retards the development and progression of CAN in type 2 diabetes.
   (d) Symptomatic orthostatic hypotension should be treated with midodrine or fludrocortisone or a combination of both in nonresponders to monotherapy.
   (e) All answers are correct.
7. Patient complains (suffers) from tachycardia and exercise intolerance. After examination anemia was diagnosed. Despite this, patient was directed to CAN testing, and CARTs were performed. Results: the deep breathing test-borderline, all others normal. Check the correct answer.

(a) Possible early CAN.
(b) Definite confirmed CAN.
(c) Severe advanced CAN.
(d) Symptomatic CAN.
(e) Insufficient information for CAN diagnosis.

8. By performing the screening of orthostatic symptoms to asymptomatic type 2 diabetic patient, a fall in systolic blood pressure of 30 mmHg and diastolic of 11 mmHg was found. The patient didn't have any other specific conditions that could lead to orthostatic hypotension. Patient was referred for CAN screening and CARTs were performed: three heart rate test abnormalities were found. What stage of CAN patient suffers from?
   (a) Possible early CAN.
   (b) Definite confirmed CAN.
   (c) Severe advanced CAN.
   (d) Symptomatic CAN.
   (e) CAN is excluded.
9. Patient with newly diagnosed type 2 diabetes mellitus and arterial hypertension had undergone ABPM test. It is also known that patient suffers from obesity and dyslipidemia. The results had shown the presence of reverse dipping. Should this patient be referred for CAN testing?
   (a) Of course patient should be referred.
   (b) CAN testing is inappropriate.
   (c) Yes, he should but in 5 years.
   (d) Just if he has clinical signs of CAN.
   (e) Yes, but after the normalization of blood pressure profile.
10. Which drugs should include pharmacotherapy of symptomatic orthostatic hypotension by CAN?
   (a) Midodrine and/or fludrocortisone.
   (b) Erythropoetin.
   (c) Desmopressin acetate.
   (d) Somatostatin analogues.
   (e) Nonselective β-blockers.

Correct Answers

1. (a) Asymptomatic patients with T2DM at diagnosis and patient with T1DM after 5 years of disease

   According to the Consensus of the CAN Subcommittee of the Toronto Consensus Panel on Diabetic Neuropathy, screening for CAN must be performed to asymptomatic patients with type 2 diabetes at diagnosis and type 1 diabetic patients after 5 years of disease, in particular those (but not only) at greater risk for CAN (level B). Screening for CAN may be also required for preoperative risk assessment before major surgical procedure (level C).
2. (e) All listed above

Risk markers for CAN are age, diabetes duration, poor glycemic control, microvascular complications (nephropathy, peripheral polyneuropathy, retinopathy), hypertension, and dyslipidemia (classes I and II). For type 1 diabetic patients, the established risk factors for CAN development is poor glycemic control (class I), and for type 2 is the combination of hypertension, dyslipidemia, obesity, and poor glycemic control (class II).

3. (a) CARTs

   Resting tachycardia may reflect diabetic autonomic dysfunction, but it also can reflect sympathetic hyperactivity and/or vagal impairment by some cardiovascular diseases, low physical activity, anemia, and other conditions. Orthostatic hypotension suggests advanced CAN that should be confirmed by CARTs (class I) but after exclusion of other pathophysiological conditions (hypovolemia, deconditioning, influence of some drugs). QTc could be prolonged due to imbalance in cardiac sympathetic innervation, intrinsic metabolic and electrolytic changes, CAD, and genetic factors. Non-dipping and reverse dipping patterns are associated with CAN, as by this conditions, vagal activity is impaired with sympathetic predominance during the night and disrupted circadian variation. So resting heart rate is not a specific sign of CAN (class IV), orthostatic hypotension (class III), QTc prolongation (class II), and reverse dipping on ABPM (class III) are specific but insensitive indices for CAN and requires CAN testing. Diagnosis of CAN is based on the use of CARTs, which are considered as the gold standard for clinical autonomic testing: heart rate response to deep breathing (standing), Valsalva maneuver, blood pressure response to standing (class II, level A).
4. (a) At least two abnormal results of cardiovascular tests/or two for borderline and three for definite

   According to the Consensus of the CAN Subcommittee of the Toronto Consensus Panel on Diabetic Neuropathy, for the definite or confirmed diagnosis of CAN is required the presence of at least two abnormal cardiovagal test results/or two for borderline, three for definite.
5. (e) All above

   According to the Consensus of the CAN Subcommittee of the Toronto Consensus Panel on Diabetic Neuropathy, all of the listened above clinical findings can alert on the presence of CAN. Especially, orthostatic hypotension suggests an advanced CAN that should be confirmed by CARTs (class I); resting tachycardia is not a specific sign of CAN (class IV), but patients with unexplained tachycardia should undergo CAN testing (level C). Qtc prolongation (class II) alone, as a reverse dipping on ABPM (class III) are an insufficient measure of CAN, but should be sign to referral for CAN testing (level B and C accordingly).
6. (e) All answers are correct

   According to the existing data, all definitions are correct. Lifestyle intervention is a basic preventive measure

(class I) and may improve HRV (level B). Resting tachycardia by CAN can be treated with cardioselective β-blockers (class I). Intensive diabetes therapy retards the development of CAN in type 1 diabetes (level A) and intensive multifactorial cardiovascular risk intervention retards the development and progression of CAN in type 2 diabetes (level B). Pharmacotherapy of symptomatic orthostatic hypotension should include midodrine (class I, level A) or fludrocortisone (level B) or a combination of both in non-responders to monotherapy (class II A).

7. (e) Insufficient information for CAN diagnosis

   Patient complaints could be explained by anemia. The presence of one abnormal cardiovagal test result identifies the condition of possible or early CAN that should be confirmed over time (level B). As the result was on borderline it is insufficient for CAN diagnosis. So, patient should undergo CAN testing after treatment of anemia.

8. (c) Severe advances CAN

   According to the Consensus of the CAN Subcommittee of the Toronto Consensus Panel on Diabetic Neuropathy, after exclusion of other causes, orthostatic hypotension suggests an advanced CAN that should be confirmed by CARTs (class I); the presence of orthostatic hypotension in addition to abnormal heart rate test (two or more) identifies severe or advanced CAN.

9. (a) Of course patient should be referred

   This patient should be referred to CAN diagnostic tests. There are several reasons to perform screening for CAN: (1) he has established risk factors for CAN development, combination of hypertension, dyslipidemia, and obesity in type 2 diabetes mellitus (class II); (2) diabetes mellitus type 2 is newly diagnosed (level B); and (3) In the presence of reverse dipping referral for CAN testing is advisable (level C).

10. (a) Midodrine and/or fludrocortisone.

    Pharmacotherapy of symptomatic orthostatic hypotension should include midodrine (class I) or fludrocortisones or a combination of both in nonresponders to monotherapy (class IIa).

    The first-line medication by orthostatic hypotension is the peripheral selective α_1-adrenergetic agonist midodrine (class I, level A). The dosing regimen should be individually tailored (the usual starting dose is 2.5 mg three times daily, most patients are controlled at or below 30 mg per day given in three or four (up to six) divided doses, but a total daily dose of 30 mg should not be exceeded. Fludrocortisone could be the first-choice drug that acts through sodium retention, a direct constricting effect on partially denervated vessels and an increase in the water content of the vessel wall leading to a reduced distensibility. In nonresponders to monotherapy, the combination of midodrine and fludrocortisone should be prescribed.

Glossary

Cardiac autonomic neuropathy Cardiac autonomic neuropathy chronic complication of diabetes mellitus is defined as the impairment of autonomic control of the cardiovascular system in the setting of diabetes after exclusion of other causes and is usually documented by using several cardiovascular autonomic reflex tests.

Cardiovascular autonomic reflex tests Cardiovascular autonomic reflex tests these tests are considered the gold standard in autonomic testing. Heart rate variations during deep breathing, Valsalva maneuver, and lying-to-standing (HR tests) are indices mainly of parasympathetic function; whereas the orthostatic hypotension, the blood pressure response to a Valsalva maneuver, and sustained isometric muscular strain provide indices of sympathetic function.

Orthostatic hypotension Orthostatic hypotension is defined as a fall in BP (i.e., >20 mmHg or more stringent criteria is >30 mmHg for systolic or >10 mmHg for diastolic BP) in response to postural change, from supine to standing.

Non-dipping status Non-dipping status a fall in average sleeping blood pressure <10% from baseline.

Reverse dipping Reverse dipping nocturnal hypertension.

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Autonomic Visceral Neuropathy and Gastrointestinal Disorders

58

Anne Mohr Drewes, Christina Brock, and Asbjørn Mohr Drewes

Chapter Objectives

- The autonomic nervous system consists of the enteric, parasympathetic, and sympathetic nerve systems. In the early stages of autonomic neuropathy, the vagal nerve seems to be the most vulnerable consequently compromising its function.
- Autonomic neuropathy is one of the most burdensome symptoms in patients with diabetes mellitus. It is, however, frequently under-diagnosed.
- In patients with longstanding diabetes, up to 40% suffer from gastrointestinal symptoms.
- Symptoms induced by visceral neuropathy cover the entire gastrointestinal tract and includes nausea and vomiting, bloating, early satiety, diarrhoea, and constipation.
- Both hyperglycaemic and hypoglycaemic episodes coalesce to form a cumulative indirect cascade which initiates and maintains neuro-inflammation in diabetic autonomic neuropathy.

Introduction

The brain–gut axis is a bidirectional nexus of the sensory input from the gastrointestinal (GI) tract and efferent pathways, which is involved in secretion of digestive hormones, homeostatic regulation, and gut motility. This axis comprises among other the autonomic nervous system (ANS), comprising the enteric nervous system (ENS), parasympathetic and sympathetic branches, which have a delicate regulatory interaction. Therefore, the ANS has an essential role, and any dysfunction leads to impaired mediation of visceral regulation. Consequently, damage to the ANS such as development of diabetic autonomic neuropathy (DAN) is one of the most burdensome complications to diabetes, yet frequently underdiagnosed. These complications cause symptoms in the GI tract such as nausea, vomiting, diarrhoea, and constipation, see Fig. 58.1. It is difficult to diagnose DAN, but it may be defined as impaired functions of the involved nerves controlling the involuntary body functions such as the cardiovascular, urinary, pulmonary, and digestive systems [1]. Cardiac autonomic neuropathy is a measureable impaired regulation of the heart function, leading to dysrhythmias, such as atrial fibrillation, tachycardia, and even cardiac arrest [2]. Patients with cardiac autonomic neuropathy develop an impaired adaptability of the heart rate, assessed as reduced heart rate variability [3], see Chap. 59 for further elaboration. In this chapter, we focus on autonomic gastrointestinal neuropathy in patients with diabetes, explaining the underlying pathophysiology and the symptomatology in the GI tract.

Diabetic autonomic neuropathy could be defined as impaired functions of nerves controlling involuntary body functions.

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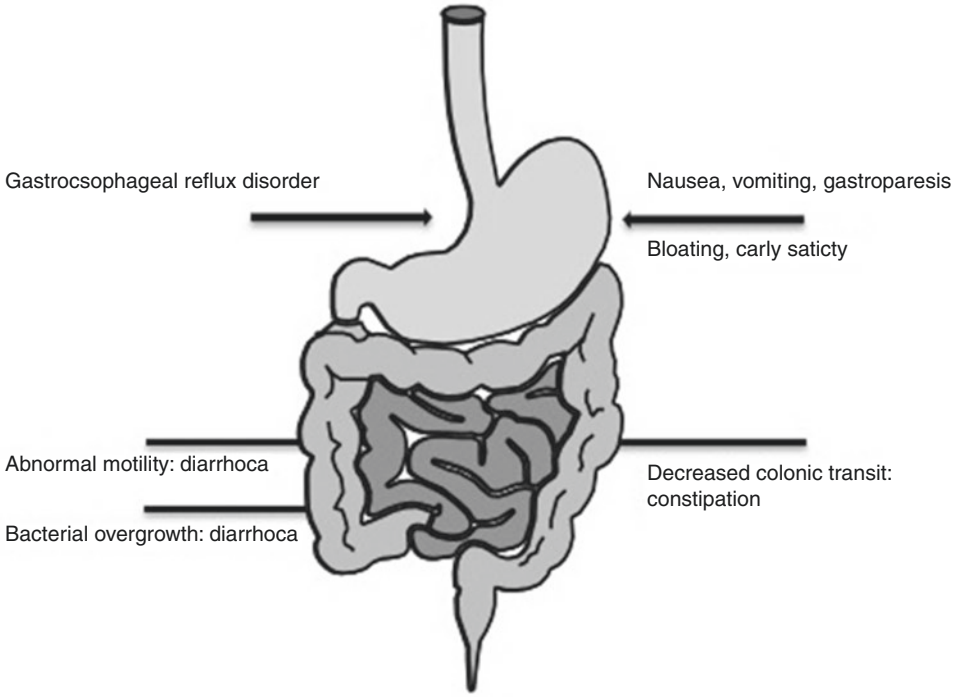

Fig. 58.1 Gastro intestinal disorders related to autonomic neuropathy

Neuropathy in Diabetes Mellitus

Neuropathy can objectively be demonstrated in 40–50% of who are diagnosed with diabetes for >20 years [4]. Recent research found evidence that in patients with long-term type 1 diabetes and polyneuropathies, there was prolonged neuronal transmission and altered neuronal brain responses at all levels of the neuraxis. The increased central conduction time was associated with diminished parasympathetic tone. This confirms that diabetes induced neuronal impairment at all levels, involving autonomic, central, and peripheral nerves [5]. It has been shown that structural changes in endoneuronal capillary morphology and vascular reactivity exist prior to neuropathy in patients with type 2 diabetes [6]. Furthermore, such endoneuronal hypoxia was associated with reductions in nerve conduction velocities. The pathophysiology underlying these findings is however complex and multifactorial and includes neuronal changes within Schwann cells, axons, and the microvascular compartment [7]. In addition, several biochemical mechanisms triggered by hyperglycaemia or hypoglycaemia also leads to neuropathy, which will be elaborated in this chapter, see Fig. 58.2.

The ENS innervates the gastrointestinal tract, gallbladder, and pancreas with motorneurons, sensory neurons, and interneurons. ENS controls the fluid transport between the gut and its lumen, local blood flow, as well as the gut motility. These functions are maintained as the ENS receive and integrate the incoming information leading to efferent transmission, which regulate the digestive system from the brainstem. Thus, there is a close connection to the central nervous system (CNS) in order to balance physiological demands. Due to the enormous amount of neurones that correspond closely to the number in CNS, the ENS is recognized as the second brain [8, 9]. All these neurones and their interconnections are vulnerable to DAN [10].

The neuronal tissue in the brain might undergo changes as well [11, 12]. Animals where diabetes has been induced showed changes in the CNS. Furthermore, functional brain imaging and electroencephalographic recordings in patients with diabetes confirm functional and structural brain changes [3]. The imaging studies demonstrated mainly microstructural changes in brain areas involved in visceral sensory processing in patients with diabetes and GI symptoms. The encephalographic studies indicated that altered insular processing of sensory stimuli could be the key player in symptom generation. In particular, one study found that the deeper the insular electrical source was located, the more GI symptoms the patients experienced [13]. Another study found that GI symptoms and beat-to-beat interval (as a proxi of autonomic tone) were correlated to reorganization in the opercular cortex. Furthermore, the shift in operculo-cingulate networks was related to decreased quality of life in the patients [14]. These studies with electroencephalography were often conducted in combination with quantitative sensory testing and mostly it was found that stimulation of the GI organs induced hyposensitivity. This is in line with patients suffering from somatic diabetic neuropathy where pain and other sensations typically are associated with hypo-

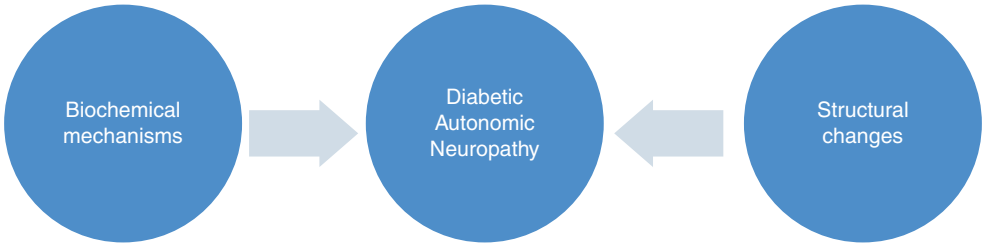

Fig. 58.2 Structural changes and biochemical mechanism triggered by hyperglycaemia or hypoglycaemia may induce visceral neuropathy

algesia to stimulation of the skin. The imaging findings and electrophysiological changes within the brain were associated with GI symptoms in patients with diabetes, therefore they might represent a biomarker for disease severity and hence be a new therapeutic target for neuromodulation or pharmacological therapy [3]. In Fig. 58.3, a conceptual model illustrating the different nerve pathways that may contribute to the GI symptoms in DM is shown.

In the early stages of DAN, alterations in the ENS are masked and difficult to detect. However, the vagal nerve due to its length and widespread appearance is most vulnerable to impaired function, and thus most work regarding DAN characterizes the vagal function [15]. The vagal nerve is the longest of the cranial nerves, and among other functions, it transmits signals from the gut wall receptors, sensitive to chemical and mechanical stimuli, controlling gut motility, secretion, and feeding behaviour [16]. Patients with diabetes and GI symptoms experience gastric retention and a delay in transit with segmentation of barium column within the small intestine, which was similar to changes found in patients with vagotomy [17, 18]. It has been shown in animal studies that the presence of glucose-responsive neurons have been identified in the CNS which may alter the vagal efferent activity [18]. Therefore, the systemic changes in blood glucose experienced in both hyper- and hypoglycaemic episodes might have a direct effect on the parasympathetic tone. Increased blood glucose level increases the level of oxidative stress and pro-inflammatory cytokines involved in neuroinflammation. Recent studies have shown that both electrical and pharmacological stimulation of the vagal nerve reduces the level of pro-inflammatory cytokines in both healthy, experimental inflammatory and auto-immune diseases [19, 20]. Hence, enhanced vagal tone might activate the cholinergic anti-inflammatory reflex and may have the potential to modulate the immune system [21, 22]. Therefore, it is plausible that enhanced vagal activity might have a protective function on diabetes-induced neuroinflammation. Taken together, the multifaceted mechanisms linked to ENS and ANS explain the variety of symptoms underlying DAN [23].

In experimental models of diabetes, reduced levels of neurotrophic support, including insulin-like growth factor and nerve growth factor, have been found. These findings have implicated reduced endoneuronal blood flow and thereby causing neuronal damage. The consequence of such

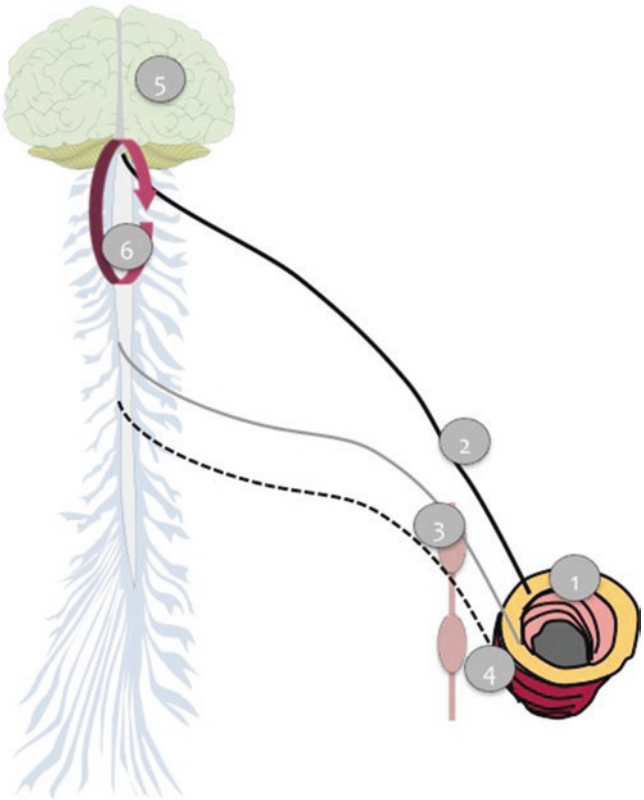

Fig. 58.3 Nerve pathways and mechanisms that may contribute to gastrointestinal symptoms in patients with diabetes mellitus: (1) Biochemical, vascular and degenerative changes in the enteric nervous system; Autonomic neuropathy that may affect (2) the vagal nerve (black line) and (3) sympathetic pathways (grey line) and indirectly modulate sensations from the gut; (4) Affection of visceral (and somatic in case the peritoneum is involved) afferents (dotted line) mediating sensations such as pain; (5) Structural and functional changes in the brain (and spinal cord), together with (6) affection of spino-bulbo-spinal loops

impairment in blood flow also leads to alteration of the nitric oxide metabolism and the Na^+/K^+ ATP-ase activity [24]. Furthermore, animal studies indicated that a changed Na+/K+ pump function may occur as a result of C-peptide deficiency. This may cause shunting glucose through the polyol pathway leading to increased levels of sorbitol and alteration of nerve excitability recovery cycle, which ultimately leads to neuronal damage [25, 26]. A last mechanism to mention is nerve damage through complement activation, as it has been reported in several peripheral neuropathies [27, 28]. A study

on chronic peripheral neuropathy in children found a cell surface deficiency of the protein CD59, which is a complement regulatory protein. Furthermore, sural nerve biopsies from patients with diabetes have shown presence of activated complement proteins and membrane attack complex neoantigen [27]. Complement activation might be a potential new area to investigate when explaining autonomic neuropathy.

The Hyperglycaemia Hypothesis

Consequences of hyperglycaemia are increased intracellular glucose level and cellular toxicity. This glucotoxicity alters cell function in different ways causing increased level of diacylglycerol (which in turn activates protein kinase C) and synthesis of polyols and hexosamines that accumulate intracellularly [29–31]. These metabolic pathways are summarized in Fig. 58.4 and is shortly explained in the following:

A minor branch of glycolysis is the hexosamine biosynthesis pathway, where fructose-6-phosphate converts to glucosamine-6-phosphate, which is a rate-limited enzyme. Hexosamine accumulate intracellular causing oxidative stress. Second, another intracellular metabolic pathway is the polyol. When the polyol pathway is activated, it may cause reduction of Na^+/K^+ -ATPase activity and osmotic damage and intracellular oxidative stress [32]. Third, increase in diacylglycerol and protein kinase C pathways is believed to increase the activity of cytosolic phospholipase A2 and produce prostaglandin E_2, as well as other pro-inflammatory mediators, which inhibit cellular (Na^+/K^+) ATPase [33, 34].

The exact mechanism by which these pathways lead to altered cell function is not fully understood, but taken together they coalesce to induce oxidative stress [35]. In the mitochondria, levels of free radicals, such as nitrogen species and superoxide rise. However, the ability to gather free radicals is reduced because of a reduction of the proton donor nicotinamide-adenine-dinucleotide [30]. Additionally, this mechanism may activate an enzyme, poly(ADP-ribose) polymerase, of great importance to deoxyribonucleic acid repair, and this activation may cause break-up of the deoxyribonucleic acid strands. The consequence of this mechanism is critically level of adenosine triphosphate in, e.g. Schwann cells, possibly leading to neuronal death [34].

When superoxide level rises, an inhibition of the key enzyme in glycolysis (glyceraldehyde-3-phosphate dehydrogenase) is manifest, resulting in enhanced activity in the involved biochemical pathways including further production of polyols, hexosamines, poly(ADP-ribose) polymerase, and advanced glycation end products, and thereby closing the loop of a vicious cycle [35]. For further reading, the following references are recommended: [36–38].

It has been found that the hyperglycaemia theory may be more valid for patients with type 1 than type 2 diabetes. Additionally, a Cochrane review found that improved glucose control prolongs the onset of peripheral sensorimotor neuropathy in type 1 DM, whereas it only had a modest, non-significant relative risk reduction in patients with type 2 DM after a follow-up period of 4 years. Contrarily, when the follow-up period was 15 years for the same cohort, the effect of increased glucose control showed significant risk reduction [39–41]. Even though these studies were conducted on peripheral axons, similar mechanisms are likely present in other nerve tissues, such as the ANS.

Finally the formation of advanced glycation end-products contribute to the intracellular non-enzymatic glycation of proteins, in which the extracellular matrix interacts with various receptors and possibly leads to pro-inflammatory gene expression that further amplifies the process [38].

The Influence of Severe Hypoglycaemia

Prolonged and severe hypoglycaemia may result in increased release of excitatory amino acids, which may cause uncontrolled triggering calcium influx. This again activates proteolytic enzymes that are known to cause neuronal damage [41]. Furthermore, hypoglycaemic levels of glucose may be counter-regulated through hormones inducing an acute rise in blood viscosity and haematocrit levels, which influences capillary blood flow especially when structural changes of the metabolic pathways and vessel of the neurons are already present [42].

Taken together, the biochemical pathways induced by hyperglycaemia and consequences of hypoglycaemia coalesce to form a cumulative indirect cascade that can initiate and summate neuro-inflammation, as is observed in DAN.

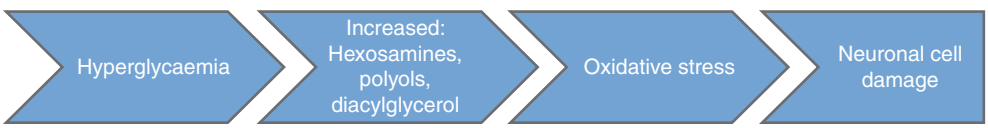

Fig. 58.4 Hyperglycaemia induces an increased level of hexosamines, polyols, and diacylglycerol within the cell, which may cause oxidative stress inducing cell damage

Gastrointestinal Disorders in Patients with Diabetes

Diabetic neuropathy may induce gastrointestinal symptoms, which will be elaborated in the following section (see Table 58.1). In several studies, patients with diabetes have reported more symptoms originating from the GI tract in comparison to people without diabetes [43–45]. Up to 20% of patients with diabetes have diarrhoea and up to 60% suffered from constipation [17, 44]. One study reported that long-term type 1 DM was accompanied by increased frequency of upper GI symptoms [46, 47]. On the other hand, another study found the prevalence of upper gastrointestinal symptoms, abdominal pain, and constipation was not significantly increased [48]. The prevalence of these symptoms varied which could have different explanations. However, due to lack of consensus, the assessment of GI symptoms varies, and thus to ensure consistency between study sites, it has been suggested to use the Diabetes Bowel Symptom Questionnaire in future epidemiological and clinical studies [49]. These disorders are difficult to treat which is why a multidisciplinary team including gastroenterologists, diabetologists, nurses, dieticians, surgeons, psychologist, and other health professionals should work together to help the patient. One main goal should be to prevent further progression by tight glycaemic control and then to ease symptoms which will be elaborated briefly in the following sections [50].

Gastrointestinal Reflux Disease

Patients with diabetes often suffer from nausea and vomiting [51]. One reason may be autonomic neuropathy-induced gastro-oesophageal reflux disease (GORD), where gastric content into the oesophagus causing complications or symptoms. Symptoms include heartburn and regurgitation. Clinical findings in GORD may also include laryngitis, chronic cough, and bronchospasm [52]. GORD could be seen in patients with DAN due to a hyperglycaemia-induced lower oesophageal sphincter pressure and increased amount of transient lower oesophageal sphincter relaxations. Furthermore, studies report that impaired relaxation of the gastric fundus might cause early satiety and dyspeptic symptoms that also influence the symptom pattern in GORD [53].

Table 58.1 Possible diabetic neuropathy-induced gastrointestinal symptoms

Diabetic neuropathy-induced symptoms
Nausea
Vomiting
Reflux
Gastroparesis
Bloating
Constipation
Diarrhoea

Patients experiencing reflux should in many cases undergo endoscopy possibly accompanied by biopsy. Acidic and non-acidic content in the oesophagus can be assessed with pH impedance monitoring, and the swallowing and sphincter functions can be investigated with oesophageal high-resolution manometry, which is especially relevant in diabetic patients where neuropathy is suspected.

Reflux treatment is individual and determined by severity and progress. First, it is important to avoid provoking factors such as large meals, coffee, and alcohol. Symptoms caused by reflux can be treated with proton-pump inhibitors, but occasionally antacids, H_2 blockers, or foaming agents are used. However, symptoms such as nausea and vomiting are mainly controlled from the brain; therefore, it is mandatory to consider dysfunction of the CNS when other causes are ruled out [3]. It is expected that the alterations in the CNS system persist even long after the primary cause (if any) is ruled out.

Gastroparesis

The most common cause of gastroparesis is diabetes, and of all cases of gastroparesis, about one-third originates from diabetes-induced gastroparesis [54, 55]. The cumulative incidence for gastroparesis is approximately 5% for patients with type 1 DM and 1% for type 2 DM [56]. Even though gastroparesis proceeds the presence of delayed gastric emptying, most research have focused on this topic, as it is present in 30–50% with long-lasting diabetes [57]. The typical patient experiencing symptomatic gastroparesis has a long history of insulin-dependent diabetes and poor glycaemic control lasting for several years. In some cases, recent onset of gastroparesis is the only diabetic complication experienced by the patient. Other symptoms may include nausea, vomiting, bloating, early satiety, and epigastric pain [58]. Furthermore, gastroparesis predisposes for small intestinal dysfunction in up to 80% of those presented with clinical symptoms, which may lead to small intestinal bacterial overgrowth or interaction between host and gut microbiota [59]. One study investigating the microbiome in patients with type 1 diabetes even indicated that the patients had a decreased diversity, reduced stability, and more classified members in their microbiome compared with healthy controls [60]. Bacterial overgrowth as well as transit problems and constipation can secondarily cause abdominal pain [61].

The detailed anamnesis is crucial when diagnosing a patient with gastroparesis, and the use of validated questionnaires, such as the PAGI-SYM, are used to assess the patient reported symptoms from which the Gastroparesis Cardinal

Symptom Index can be calculated [62]. To investigate a gastroparetic patient, gastroscopy is often needed to rule out differential diagnosis such as celiac disease, ulcers, and cancer. If symptoms resemble those seen after truncal vagotomy (mild gastric dilation, poor to no peristalsis, residual gastric secretions despite a prolonged fast, atonic duodenal bulb, and open pylorus), then the diagnosis is straightforward. However, a proportion of these patients have no gastroscopic abnormalities [17, 63]. In such cases, motility investigations such as scintigraphy or radiopague markers are needed [64]. Scintigraphy is in most laboratories the "gold standard" to assess gastric emptying time, where retention of a meal labelled with ^{99m}Tc sulfur colloid is compared to normal reference values [57]. Recently, the wireless motility capsule (such as the SmartPill), which consist of a portable receiver, a wireless transmitting capsule, and displaying software has been taken into use. Following consumption of a standard meal, the participant swallows the capsule, which samples and transmits pressure, pH, and temperature data, from which segmental transit times (including gastric emptying time) can be derived [65, 66]. Alternative tests to asses gastric emptying include breath tests which measures the non-radioactive isotope ^{13}C labelled digestible substance and measure the metabolized isotope in the breath, emptying of radiopaque markers from the stomach by use of fluoroscopy, ultrasonography, ultrasound, and the paracetamol absorption test which is valid for gastric emptying of liquid meals [57, 64, 67–70].

The treatment of gastroparesis is challenging, but patients should be encouraged to focus on glycaemic control. The antiemetic drug metoclopramide has shown control of symptoms in 30–60% of patients and domperidone has shown effective in up to 60% of cases [71]. However, it must be underlined that there is no association between symptom improvement and changes in gastric motility following treatment with prokinetics [72]. Furthermore, most prokinetics are limited to short-term use due to the risk of irreversible tardive dyskinesia and cardiovascular side effects. Furthermore, symptoms can be diminished by use of pharmacological agent that increases motility such as erythromycin or (off label) prucalopride. New molecular targets are currently identified, and relamorelin, a synthetic ghrelin analogue, has shown promising results accelerating gastric emptying [73]. Endoscopic procedures such as botulinum toxin injections and myomectomy of the pylorus are also promising [61]. Constipation—if present—should also be adequately treated as it may give "upstream" motility disorders.

Another important aspect is nonpharmacological treatment with dietary consulting to improve glycaemic control [61]. In theory, patients with concomitant functional disorders or bloating may benefit from Low Fermentable Oligo-, Di-, and Mono-saccharides and Polyols diet (low-FODMAP) [74]. It is a dietary intervention under investigation in dysmotility disorders, which is why it might benefit selected diabetic patients with neuropathy-induced dysmotility [75]. Avoidance of these carbohydrates should be global, and it is important to recognize that ingestions of FODMAPs are not the cause of the disease, but limited intake may represent an opportunity to reduce the patient symptoms [74]. Another dietary intervention has been studied by Olausson EA et al. [76]. In this study, patients with diabetes mellitus and gastroparesis were to eat a small particle diet. They found that patients on this diet improved in key symptoms such as nausea and vomiting. Furthermore, gastric electrical stimulation has been approved by the US Food and Drug Administration to alleviate symptoms in gastroparesis. The underlying mechanisms are debated and a growing body of evidence points toward alteration of the sympatico–vagal balance rather than enhancing gastric motility [77]. Nonetheless, the procedure has shown to decrease both symptom frequency and severity [78]. A potentially new method is stimulation of the vagal nerve during the skin together with deep breathing. This has been shown to increase gastric contractions in healthy volunteers [79], and currently a study is undergoing to explore this method in patients with diabetes [80].

Diarrhoea

Diarrhoea is observed in up to 20% of patients. The diarrhoea can be present as episodic, loose stool consistency, and periods with normal bowel function alternating with constipation [17, 59]. The cause of idiopathic diabetic diarrhoea is not known; however, the most recognized explanation is shifted sympatico–vagal balance as both sympathectomy and truncal vagotomy can cause diarrhoea. It may be caused by rapid transit or slow transit together with bacterial overgrowth [59, 81]. Even though autonomic neuropathy often induce prolonged transit times, it may also indirectly cause diabetic diarrhoea [17]. Furthermore, a study found that long-standing diabetes was associated with a decrease in number of interstitial cells of Cajac as well as decreased inhibitory innervation and an increase in excitatory innervation causing diarrhoea [82].

Abnormal and dis-coordinated motility of the small bowel may also lead to small intestinal bacterial overgrowth, which potentially also causes diarrhoea [83]. Third, faecal incontinence due to *anorectal dysfunction* can be present due to a weakened internal anal sphincter and lowered rectal sensory threshold [84]. Finally, as insulin is a trophic hormone for the acinar and ductal cells in pancreas, *pancreatic exocrine insufficiency* must be considered, especially when steatorrhoea is found, and as a parallel, patients with pancreatitis may have demolished the visceral nerves [85]. Appropriate test with pancreatic enzyme therapy or pancreatic function test is recommended.

Diagnosis of neuropathy-induced diarrhoea serves to exclude differential diagnosis that can lead to chronic watery diarrhoea, for example microscopic colitis or irritable bowel syndrome. If differential diagnosis can be excluded, the diagnosis idiopathic diabetic diarrhoea can be made (non-specific radiological findings and clinical symptoms) [17].

In order to treat patients with severe and long-lasting diabetic neuropathy-induced diarrhoea, there are six important targets: (1) hydration, nutrient deficiency, and correction of electrolyte deficiencies, (2) fibre supplementation which might be helpful in some cases, however it may also worsen gastroparesis, (3) symptomatic treatment with, e.g. codeine or loperamide as antidiarrheal medication by prolonging transit time and reduction of peristalsis, (4) treatment of underlying causes such as bacterial overgrowth with probiotics/antibiotics, (5) enzyme supplementation in case of exocrine pancreas insufficiency [71], and (6) glycaemic control in order to reverse underlying mechanisms [86].

Constipation

Motility disorders, more specifically reduced colonic transit time due to dysfunction of the ENS and ANS leads to constipation [53, 87]. A study investigating the prevalence of constipation in diabetics showed that 60% reported constipation and thus it is the most commonly reported symptom. Furthermore, the same study reported that 76% of the patients suffered from at least one GI symptom [17]. Furthermore, reduced bowel motility may result in specific constipation that occasionally leads to overflow incontinence that influences the clinical picture [71]. Of note, 80% of patients with diabetic diarrhoea also suffered from periods with constipation.

Constipation can be evaluated with radiopaque markers, scintigraphy, or different capsules as mentioned above and recently reviewed in [65]. In patients with functional gastrointestinal disorders, a reduction in caecal and colonic contractility, as well as bloating and distension was associated with excessive fermentation in the caecum assessed as a higher pH-drop across the iliocaecal junction [88]. A recent study found that patients with type 1 diabetes had prolonged small bowel transit, colonic transit, gastric emptying, and whole-gut transit time compared with healthy controls. Furthermore, prolonged colonic transit time in association with an increased fall in pH across the ileocecal junction was found [66]. Similar findings were shown in a recent paper where the wireless motility capsule was used to show panenteric prolongation of gastrointestinal transit times and a more acidic caecal pH, which may represent heightened caecal fermentation in diabetics [66].

Constipation could be due to alterations in the microbiota—or vice versa—however the exact mechanism on how alterations in microbiota influences the colonic motility. One study indicates that the breakdown of short chain fatty acids induces acidic milieu and thus modifies motility rhythm in the hindgut [89]. In support of this, animals who received antibiotics were shown to modulate their gut microbiota, which consequently improved their glucose tolerance and sensitivity to insulin [90]. Similar mechanisms are plausible in humans but need to be investigated in further detail.

Constipation may be treated conservatively with regular exercise, increased intake of dietary fibres, and focus on hydration. A non-pharmacological vibrating capsule has reduced constipation by improving peristaltic waves in the large intestine, however further studies are needed. Medical interventions may include bulk fibres or laxatives. In patients with slow-transit constipation, it is preferred to use osmotic laxatives compared to fibre supplementation and bulking agents. As the latter stimulates the intestines to absorb excessive amounts of fluid from the body. Frequently, osmotic active drugs are also used in combination with enemas. The reader is referred to [50, 61, 91].

In chronic constipation due to autonomic neuropathy and slow transit newer drugs such as prucalopride, a selective 5-HT receptor agonist may prove to be useful as it enhances colonic transit. Furthermore, lubiprostone stimulates secretion of electrolyte secretion and colonic water through activating of type 2 chloride channels in enterocytes. Another plausible target in the future is altering the composition of the microbiota through dietary alterations or faecal transplantation.

Diagnosis of Diabetic Autonomous Neuropathy

The clinician should ideally investigate the GI symptoms as described in section "Gastrointestinal Disorders in Patients with Diabetes" of this chapter. Additionally when gut symptoms arise in patients with diabetes, autonomic neuropathy should always be suspected, especially if the patient also suffers from distal symmetric polyneuropathy. Conventional measures of the autonomic function are indirect methods that rely on cardiovascular reflexes. However, the detection of early and subtle abnormalities in the parasympathetic system remains controversial, as the methods are relatively insensitive to sympathetic deficits [1, 92]. Classically, the ANS function has been correlated to recordings of the peroneal nerve [1, 93]. However, these methods are unspecific, invasive, and time consuming, which could explain why the most popular and the most utilised is time domain derived parameters of Heart Rate Variability or sudomotor reflex testing. One way to measure real-time brainstem vagal efferent activity known as cardiac vagal tone is with the neuroscope. A non-invasive measurement using ECG electrodes to

detect phase shift in the beat-to-beat RR interval, which is described in detail elsewhere [94]. Another method in the future may be to measure potential biomarkers such as N-acetylaspartate with magnetic resonance imaging, which have been found to be reduced in patients with type 1 diabetes and central neuronal dysfunction or loss [95]. However, diagnosing DAN remains complicated as there is poor association between autonomic function testing and experienced GI symptoms [1].

There is no consensus regarding the optimal test parameters [96–98], and the shortcomings of each methods and their interpretation is responsible for the lack of formal diagnosing of DAN. Thus, such diagnosis is frequently delayed, the causes of which are most certainly multifactorial but arguably includes the non-specificity of presenting symptoms, the lack of clinician appreciation, and the limited availability of specialised diagnostic services. Nevertheless, diagnosis of DAN is important as it has a pivotal role in the pathophysiology of a number of diabetes-induced complications.

Concluding Remarks

Manifest DAN is one of the most burdensome symptoms, yet frequently under-diagnosed. The autonomic neuropathy induces symptoms such as nausea, vomiting, bloating, early satiety, diarrhoea, and constipation, which undoubtedly compromise the quality of life in these patients. The frequently presence of GI symptoms in patients with diabetes should make the clinician focus on DAN. Conservative and symptomatic treatment should accompany the suspicion of DAN, and if possible, the underlying cause should be treated. Ideally, treatment should be individualised as the symptom complex differs between patients. New emerging therapies are in pipeline and future research will undoubtedly result in improvement of the armamentarium clinicians have available for treatment of the severe complications associated with DAN.

Multiple Choice Questions

1. The autonomic nervous system comprises.
   (a) The sympathetic, parasympathetic branch.
   (b) **The enteric nervous system, parasympathetic, and sympathetic branches.**
   (c) The sympathetic branch.
   (d) The parasympathetic and enteric nervous system.
   (e) The brain, the so-called second brain "the enteric nervous system" and the sympathetic branch.
2. In patients with longstanding diabetes up to how many percentage of the patients suffer from GI symptoms such as nausea and vomiting.
   (a) 10%
   (b) 12%
   (c) 20%
   (d) 25%
   (e) **40%**
3. Which part of the gastrointestinal tract can be affected by visceral neuropathy?
   (a) The upper GI tract.
   (b) The lower GI tract.
   (c) The bowel.
   (d) Only the anorectal part of the GI tract.
   (e) **It is possible that the neuropathy cover the entire gastrointestinal tract causing symptoms such as nausea and vomiting, bloating, early satiety, diarrhoea, and constipation.**
4. In order to treat patients with reflux which statement is most correct?
   (a) The only treatment is avoiding provoking factors such as large meals.
   (b) The only treatment is medical including combinations of antacids and proton pump inhibitors.
   (c) **First, it is important to avoid provoking factors such as large meals, coffee, and alcohol. Symptoms caused by reflux can be treated with antacids, H_2 blockers, proton pump inhibitors, or foaming agents.**
   (d) Constipation treatment should be the first option.
   (e) Currently no treatment exists.
5. The typical patient experiencing symptomatic gastroparesis is?
   (a) A newly diagnosed type 1 diabetic.
   (b) **A patient with a long history of insulin-dependent diabetes and poor glycaemic control lasting for several years.**
   (c) A diabetic with extreme alcohol abuse.
   (d) A newly diagnosed type 2 diabetic.
   (e) A patient with a long history of well-controlled diabetes.
6. Hypoglycaemia has been shown to cause cell damage, but how?
   (a) It increases levels of NO in the entire body.
   (b) Unhealthy levels of calcium leaves the cell.
   (c) Reduction in release of excitatory amino acids protecting the cell.
   (d) **Increased release of excitatory amino acids, which may cause uncontrolled triggering calcium influx. This again activates proteolytic enzymes that are known to cause neuronal damage.**
   (e) The production of reactive oxygen species is limited.

7. In order to treat patients with diabetes and diarrhoea, which statement is most correct?
   (a) **Hydration, nutrient deficiency and correction of electrolyte, antidiarrheal medication to prolonging transit time and reduce peristalsis, as well as reducing faecal volume in order to control symptoms, treatment of the underlying cause.**
   (b) Antidiarrheal medication for 1 week.
   (c) Hydration, nutrient deficiency and correction of electrolyte, and treatment of underlying cause such as bacterial overgrowth which should be treated with antibiotics.
   (d) Hydration, nutrient deficiency and correction of electrolyte, and treatment of underlying cause such as anorectal dysfunction.
   (e) Surgery of the intestines.
8. Which of the following statements about the pathophysiological explanation behind visceral neuropathy is most correct?
   (a) Hyperglycaemia is the only main player in inducing oxidative stress.
   (b) Hypoglycaemia is the only main player in pro-inflammatory mechanism.
   (c) Hyperglycaemia and hypoglycaemia are the only main players in inducing neuronal damage.
   (d) **Peripheral and autonomic neurons, as well as their interconnections, are particularly vulnerable to hyperglycaemia. It is obvious that any increase in glucose is associated with increased risk of injury to the organ including neuropathy.**
   (e) Hyperlipidaemia is main player alone to induce oxidative stress and pro-inflammatory mechanisms.
9. The measurements of GI symptoms have varied in many studies. What should researcher be aware of in future studies?
   (a) Every patient with gut symptoms should be offered an upper endoscopy locating symptoms.
   (b) Every patient with gut symptoms should be offered an upper endoscopy as well as a colonoscopy to investigate the entire gastrointestinal tract.
   (c) **In future epidemiological and clinical studies, the Diabetes Bowel Symptom Questionnaire is suggested as a consistent method to measure GI symptoms.**
   (d) A computed tomography scan of the body should be conducted in order to cover every symptom in patients with diabetes.
   (e) The variation is unavoidable and must be accepted.
10. When should autonomic neuropathy be suspected in patient with diabetes?
   (a) When newly diagnosed.
   (b) When the patients asks about it without symptoms.
   (c) **When gut symptoms arise, especially if the patient also suffers from distal symmetric polyneuropathy.**
   (d) When changing medicine.
   (e) Always.

Further Reading

1. Feldman M, Schiller LR. Disorders of gastrointestinal motility associated with diabetes mellitus. Ann Intern Med. 1983 Mar;98(3):378-84
   – Provides an overview of gastrointestinal symptoms in patients with diabetes
2. Rayner CK, Samsom S, Jones KL, Horowitz M. Relationships of Upper Gastrointestinal Motor and Sensory Function With Glycemic Control. Diabetes Care. 2001 Feb;24(2):371-81
   – A great article to read if you wish to know more about the effect of acute change in blood glucose toward the upper gastrointestinal tract.
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   – This article provides a thorough knowledge about gastroparesis in relation to diabetes.
4. Brock C, Brock B, Pedersen AG, Drewes AM, Jessen N, Farmer AD. Assessment of the cardiovascular and gastrointestinal autonomic complications of diabetes. World J Diabetes 2016 Aug 25;7(16):321-32. doi:
   – This article is recommended as further reading if one is interested in knowing more about the cardiovascular system and the gastrointestinal tract in relation to DAN.

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Urologic Complications in Patients with Diabetes

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Introduction

Diabetes Mellitus (DM) is a group of metabolic diseases associated with high glucose levels that cause systemic long-term damage, dysfunction, and failure of several tissues [1]. Among the consequences of this chronic hyperglycemic state, patients with DM suffer several urologic complications that involve endothelial and neural damage all along the genitourinary tract with significant economical and quality-of-life costs.

The worldwide incidence of urologic complications associated with DM is increasing because of the high incidence of obesity in the entire world [2]. The effect of obesity in our society is growing at a worrying rate, and it is associated with an increasing risk of noninsulin-dependent diabetes. Clinicians have the opportunity to prevent, diagnose, and change the evolution of these urologic complications among patients with diabetes by maintaining a proper weight [3].

Diabetes has been associated with an earlier presentation and increased severity of urologic complications [4]. DM leads to nerve function disturbance, loss of innervation of neuromuscular nerve terminals, abnormal immune response, and altered sympathetic/parasympathetic innervation [5]. Therefore, peripheral accumulations of fat in the abdominal region of patients with diabetes has been associated to an increased risk of urologic complications such as urinary incontinence, erectile dysfunction, benign prostatic hyperplasia, urinary tract infections, and possibly with cancer [3].

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Bladder Dysfunction (BD) and Cystopathy

Generally, the beginning of bladder lesions of diabetes is not very evident, and they are not recognized until the disease is in the most advanced stages. Between 20 and 50% of all diabetic patients are affected, although some studies raise this figure to 88% of cases. No correlation has been observed between the type and duration of diabetes or the age of the patients, although it was shown that 80% of cases with a neurogenic diabetic bladder have lesions in other organs (kidney, eye, penis, arteries, etc.). (Campbell-Walsh 12 ed).

Bladder dysfunction or dysfunction in the bladder outflow tract attributed to any alteration of the nervous system. Some bladder symptoms that occur in patients with diabetes mellitus are known as diabetic bladder dysfunction or diabetic cystopathy, which include lower urinary tract symptoms (LUTS) characterized by increased postvoid residual volume due to inadequate emptying of the bladder, resulting in increased bladder capacity, worsened by reduced sensation and contraction of the bladder [6].

The cornerstone for evaluation is the questioning of urologic history, sexuality, bowel behavior, and neurologic history. Within the specific urological history, we must take into account the onset of symptoms, relief after urination, the beginning and end of urination, if there is presence of interruption of urination, mode and type of urination, enuresis and a strict record is essential in a urination diary.

Almost half of patients with DM suffer from different degrees of bladder dysfunction (74% men and 59.26% women), which causes an increase in postvoid residual urine and urinary incontinence, causing infections, bladder stones, or eventually kidney damage [7]. In men, bladder disorders are made worse by the enlargement of the prostate associated with age.

In Mexico, approximately 12% of the population suffers from type 2 diabetes mellitus, so the prevalence of bladder dysfunction due to this cause is common in the urological delivery, it is important to know how to detect it and refer it in time to the urology specialist to its timely treatment.

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Obese and diabetic women are expected to have more pelvic floor disorders, such as stress urinary incontinence and overactive bladder [4] that could be related to increased abdominal pressure from the abdominal panniculus that exerts pressure unwanted over the pelvic organs, uterus, bladder, urethral sphincters and vagina [3], peripheral neuropathy, and loss of bladder support. Insulin treatment in women with diabetes mellitus increases the risk of urge incontinence, compared to women treated with metformin, which has no effect on incontinence [8, 9].

Bladder hypersensitivity is reported as the most common finding, ranging from 39% to 61% in patients with diabetes mellitus, in numerous clinical studies [6]. Furthermore, an important predictor of bladder dysfunction is the presence of peripheral neuropathy, renal disease, and the association of metabolic syndrome [4].

Pathophysiology

During the early stages of diabetic cystopathy, there is an increase in the storage capacity of the bladder, which affects its compliance or ability to adapt to pressure as the bladder fills [10]. Several mechanisms have been described that induce abnormalities in bladder function at the detrusor muscle level, including changes in intracellular connections and excitability, muscarinic receptor density, genetic traits, and changes in intracellular signaling. All of these contributing factors result in decreased contractility and increased postvoid residual volume. Compensatory bladder hypertrophy results in increased bladder instability that decreases its contraction force due to collagen deposits, rendering detrusor muscle tension ineffective [10]. Another theory is the associated increase in diuresis due to the hyperglycemic state resulting in neural and endothelial damage, which collectively can lead to detrusor muscle hypertrophy in an attempt to adapt to these changes. On the other hand, abnormalities in calcium and potassium cell wall channels increase detrusor muscle activity and increase hyperactivity [11]. Furthermore, rabbit models have shown that overexpression of aldose reductase and increased lipid peroxidation products result in decreased detrusor contractility [12].

Another problem that influences bladder hypertrophy could be an increase in oxidative stress, associated with greater damage to the bladder muscles [13] or induced by a deficiency in axonal transport of neural growth factor (NGF). Bladder tissue remodeling is also associated with downregulation of tissue growth factor (TGF) and collagen mRNA levels, which induce an increase in elastin synthesis. These factors can result in an increase in bladder compliance in patients with diabetes associated with a reduction in collagen synthesis [14].

Neuronal control of bladder function consists of an interaction between autonomic sympathetic and parasympathetic, somatic afferent and efferent pathways. Patients with diabetic cystopathy have somatic and autonomic neuropathy. In addition, cells subjected to long periods of exposure to hyperglycemia suffer an accumulation of oxidative stress products, which cause axonal degeneration and nerve damage, decrease nerve conduction, trigger diabetic cystophaty, and erectile dysfunction [15]. In addition, decreased bladder filling sensation, caused by nerve damage, can cause excessive distention and increased hypocontractility of the bladder wall in diabetic patients. Diabetic cystopathy also involves neuropathic changes, produced by hyperexcitability of the urethral afferent reflex, leading to external urethral sphincter dysfunction and reduced urethral smooth muscle relaxation with obstruction to urine outflow.

Long-standing diabetes also affects the peristaltic function of the ureters by interfering with ureteral muscle cells and nerve function, causing upper urinary tract dysfunction, urine stasis, and eventually kidney stone formation [5]. The voiding reflex is a neural stimulus controlled by the M2 and M3 receptors. Patients with diabetes have a greater number of muscarinic receptors in the urothelium that increase sensory nerve activity and modify detrusor contraction, causing greater bladder dysfunction and urinary stasis [11].

Clinical Manifestations

In the early stages of the diabetic bladder, compensatory changes maintain the ability to maintain a normal diuresis. In later stages, decreased voiding pressure and increased urethral obstruction lead to larger volumes of postvoid residual urine, producing a wide variety of symptoms ranging from urgency to urinate and incontinence (a sensation urinary leakage) (40% to 80% risk) to the most severe expression of overflow incontinence (in which the bladder empties due to excess residual urine without patient control) [16].

Diabetic patients can complain of lower urinary tract symptoms, including urgency, difficulty in initiating, maintaining and ending urination, inadequate voiding or sensation of residual urine, frequent urination during the day and night, slow or decreased urinary flow of different severity levels. Consequently, voiding reflexes appear to be diminished or inactive, causing a progressive asymptomatic increase in bladder capacity, which can eventually cause urinary retention, bladder stone formation, diverticula, infection, upper urinary tract dilation, and kidney damage. . In contrast, diabetic bladder dysfunction can also present as overactive bladder syndrome with corresponding frequent day and night bladder emptying, urgency, and lower urinary tract symptoms. Hypersensitivity and hypercontractility of the bladder are more common than hypocontractility [6].

Diabetic cystopathy and bladder dysfunction are common in long-standing diabetic patients. They can be asymptomatic or manifest a wide spectrum of clinical symptoms, ranging from voiding discomfort due to overactive bladder and urge incontinence due to decreased bladder sensation, to overflow incontinence and acute urinary retention [4]. Bladder symptoms can be divided into irritating and obstructive. Irritant symptoms involve the overexcited detrusor muscle, causing urgency, polyakiuria, nocturia, and urge incontinence, known as overactive bladder syndrome. Obstructive symptoms include decreased size and strength of voiding flow, terminal dribbling, decreased sensation of a full bladder, and high postvoid residual urine. Obstructive symptoms are related to a pseudo-obstructive bladder, represent the last phase of visceral diabetic neuropathy, and are associated with a low urine flow that can be demonstrated with uroflowmetry, high postvoid residual and urodynamic studies, which show a hypotonic bladder in cystometry caused by a myogenic alteration of the microvasculature and neuronal cells. [10, 17].

Diagnosis

The approach to the study of diabetic cystopathy depends on the individual patients symptoms, severity, renal function, and impact on quality of life. In patients with symptoms of bladder dysfunction, physicians should take a detailed history including the International Male Prostate Symptom Score, physical examination with neurological reflex and rectal examination, presence of pelvic organ prolapse, followed by tests of laboratory to evaluate kidney function (serum creatinine), infections (urine test), and clinical chemistry. Similarly, a sexual history, the presence of genital or sexual dysfunction, the sensation in the genital area, specific to the man (erection, orgasm and ejaculation) and specific to the woman (dyspareunia and orgasm), within the habits bowel movements, presence of fecal incontinence, urgency, rectal sensation, stool pattern, and the onset of this complication. In the neurological history, if you have a congenital or acquired condition, mental status, neurological symptoms, spasticity, or autonomic dysreflexia.

The diagnosis of diabetic neurogenic bladder is based on the performance of a complete urodynamic study (flowmetry, cystometry, electromgraphy, and urethral pressure profiles). The most common findings of the final stages of the disease are the loss of voiding sensation with significant increase of bladder capacity and decreased detrusor contraction (areflexia) with low voiding flow and presence of residual postvoiding urine. The picture must be differentiated from infravesical urinary obstruction, which is achieved with a pressure/flow study. Urodynamic evaluation is an essential component of the examination, although it is not indicated in all cases. It includes cystometrogram, simultaneous flow and pressure studies, sphincter electromyography, and postvoid residue measurement [6]. It is recommended that the patient has to carry out a voiding diary prior to the urodynamic study. Diabetic women have significantly higher nocturia scores on lower urinary tract symptom questionnaires, with weaker urinary flows, reduced voiding volumes, increased residual urine volumes, and lower peak flow rates by uroflowmetry [4].

Treatment

The first step in managing any type of diabetes complications is blood glucose control. The treatment of diabetic cystopathy depends on the severity of the symptoms, but in the early stages, it is basically conservative and, in case of complications, they should be treated accordingly [18]. The treatment of diabetic neurogenic bladder resides in the treatment of symptoms, the prevention of urinary infection, the maintenance of renal function, and continence with an adequate bladder emptying. However, there is no cure for the disease. When there is an unstable bladder, the use of anticholinergics is of great help to improve symptoms (Campbell-Walsh 12 ed). In patients who complain of urgency, different types of first-line therapy are available to control detrusor overactivity, including oral muscarinic drugs, and more uroselective anticholinergics with fewer adverse effects (oxybutynin, tolterodine, darifenacin, or solifenacin). A recently approved β3 adrenergic agonist (mirabegron) that increases urine storage capacity, by direct relaxation of detrusor smooth muscle, can be used to provide rapid relief of symptoms [19, 20]. Infiltration of the detrusor muscle with botulinum toxin has been shown to decrease urge incontinence. A surgical approach could be offered in severe cases of unresolved urge incontinence with selective muscarinic anticholinergics, including bladder denervation, myomectomy, and bladder augmentation with ileal cystoplasty. All of them are associated with the risk of increased postvoid volume, urinary tract infection, kidney damage, and stone formation [18].

In men with additional bladder outlet obstruction associated with an enlarged prostate, initial treatment includes the use of alpha blockers such as terazosin, tamsulosin, and alfuzosin. In advanced stages, transurethral resection of the prostate could be considered.

In cases of failure to empty the bladder, frequent clean intermittent catheterization is the best option to avoid permanent use of indwelling catheters, due to the risk of increased infection rate, lower urinary tract lithiasis, and squamous cell carcinoma of the bladder [21].

All these measures are always carried out to protect kidney function, since, by increasing bladder pressure, due to the increase in urinary volume and the lack of accommodation of the bladder, they can cause a deterioration in kidney

function and worsen the damage per se. That is what diabetes mellitus does to the kidneys (Campbell-Walsh 12ed.). Similarly, within the objectives of treatment, they are to avoid urinary tract infection, achieve or maintain urinary continence, preserve the ability to urinate, and improve the quality of life of the patient.

Benign Prostatic Hyperplasia (BPH) and Urethral Obstruction

Benign prostatic hyperplasia (BPH) is an age-related phenomenon that affects up to 50% of men aged 60–69 years and almost 90% at age 90 [22]. DM is frequently associated with BPH due to the same age of incidence [23]. BPH has been largely associated to metabolic disorders including diabetes, metabolic syndrome, obesity, and hypertension. Preclinical and clinical studies have shown that increased plasma insulin levels are positive independent predictors of BPH, as well as high fasting glucose level and hyperlipidemia; all of them have shown a positive correlation to the progression of BPH [24–26].

Pathophysiology

Several theories have been proposed in the pathogenesis of BPH. The most convincing however is that prolonged chronic ischemia and repeated ischemia-reperfusion injury in the bladder could generate oxidative stress, which increases sympathetic nerve activity and vascular damage, further hypoxia of the bladder and prostate, abnormal cell proliferation, in addition to an increase of lower urinary tract symptoms [22]. Endothelial dysfunction and nitric oxide (NO) deficiency are among the most important factors in the development of diabetic complications, affecting the lower urinary tract as well. Relaxation of the urethral sphincter is partially affected by NO, which in turn causes outflow obstruction and hyper-excitability of afferent neurons associated with progression of diabetes [27]. All these factors, in addition to the increased risk of overactive bladder in diabetic patients are closely related to peripheral nerve irritation [28]. Another possible explanation for the presence of BPH in diabetic patients involves insulin-like growth factor (IGF). Beta cells of patients with Type 2 diabetes secrete higher concentrations of insulin; the resulting hyperinsulinemia stimulates IGF synthesis. Activation of the prostate IGF receptors may also cause prostate growth [29, 30] which could be explained because of homology of insulin and IGF receptors [31] and cross-activity to insulin action [32].

The pathogenesis of BPH is multi-factorial and characterized by basal cell hypertrophy, secretory alterations of luminal cells, infiltration of lymphocytes with production of pro-inflammatory cytokines, stromal proliferation, diminished apoptosis, trans-differentiation and extracellular matrix production, abnormal autonomous innervation, and modification of the neuroendocrine cell function among others [22]. Disturbances in fatty acid metabolism are also influential in the progression of BPH, including inflammation, oxidative stress, peroxidation of lipids and accumulation of 8-hydroxy-2′-deoxyguanosine, and increased androgen synthesis [33].

Clinical Manifestations

Initially, patients with BPH complain of symptoms of LUTS (which already mentioned includes nocturia, frequency, urgency, weakened stream, hesitancy, intermittency, straining, and a sense of incomplete emptying) [34]. Progressive evolution toward complications in the urinary tract is more important than symptoms related to micturition. They are significant and include bleeding, lithiasis, renal insufficiency, and infections [35], but the most serious and painful manifestation is acute urinary retention, the inability to urinate, characterized by intense pain in the pelvis [36].

Diagnosis

Evaluation of BPH in diabetic patients includes a detailed medical history, including LUTS questions, severity, and influence in their quality of life. The American Urological Association Symptoms Index (AUA-SI) is a questionnaire that allows physicians to quantify symptoms at diagnosis and over time in response to treatment. Digital rectal examination should be included in the physical examination. PSA (Prostate-specific antigen), urinalysis, and frequency/volume chart may be filled, as well as uroflowmetry, post void residual ultrasound, and renal ultrasound in order to diagnose complications [34].

Treatment

To avoid complications, effective and conservative drug treatment for BPH is currently available. Patients with a small prostate are routinely treated with alpha-1 blocker monotherapy as first-line therapy, either with nonselective blockers such as doxazosin and terazosin or uroselective blockers such as tamsulosin, alfuzosin, and silodosin. All of them have similar effectiveness but diverse side-effect profiles. Characteristic side effects include postural hypoten-

sion, dizziness, rhinitis, asthenia, sexual dysfunction, and abnormal ejaculation. Storage and voiding symptoms improve briefly after initiation of treatment. Alpha-1 blockers do not prevent BPH progression. For that reason, prostate volume and symptom progression should be monitored during the follow-up of the patient [34, 37].

Patients with a small prostate associated to voiding symptoms, the diagnosis of overactive bladder should be considered and treated as previously mentioned with anticholinergics, keeping in mind the need to monitor by dynamic bladder ultrasound the possibility of urinary retention, even though the risk is low.

In patients with enlarged prostate (over 30–40gr), the use alpha-1 blockers in combination with an alpha 5 reductase inhibitor (finasteride or dutasteride) that block the conversion of dehidrotestosterone from testosterone is highly recommended, in order to diminishing the prostate volume at long term with a faster effect on the relaxation of the bladder neck. In case of failure with all these therapies, the surgical approach is the next option. Transurethral resection of the prostate is the gold standard, but newer techniques such as bipolar resection, and the use of laser vaporization, botox infiltration, cryotherapy and high intensity focused ultrasound among others, represent less invasive approaches than open adenomectomy [36, 37].

Sexual Dysfunction

Men and women with diabetes are affected by sexual dysfunctions, which are defined as the inability to achieve or maintain an adequate sexual response to complete a sexual encounter or intercourse resulting in a satisfactory orgasmic sensation. Sexual dysfunctions include disorders of libido, ejaculatory problems, orgasmic abnormalities, and erectile dysfunction. The reported prevalence of sexual dysfunction in men with type 2 diabetes is up to 46%. Sexual dysfunction in women is harder to diagnose but it has been proposed that its prevalence in type 1 diabetes is 71% and 42% in females with type 2 diabetes [38, 39].

Almost half of nonsexually active men and women with type 2 diabetes report that their sexual life do not fulfills their sexual needs, suggesting that they are more concerned and even more distressed than sexually active patients. Commonly, women argue that lack of sexual activity is related to a number of reasons, including lack of interest, physical problems that make it difficult or unpleasant, absence of partner, or having a partner with physical limitations [40].

Sexual dysfunctions involve a group of alterations that affect significantly the quality of life of these patients and include reduced desire, decreased arousal, orgasmic abnormalities, and painful intercourse [41].

Leading risk factors that further affect diabetic men and women include age, length of diabetes [40] co-medications, obstetric history, neurogenic and vascular complications, and infections among others.

Erectile Dysfunction (ED)

It is defined as a long term, consistent, or recurrent inability to attain and/or maintain penile erection sufficient for sexual satisfaction. It is the third most frequent complication of diabetes and considered as one of the most significant complaints affecting quality of life [42]. Manifestations usually appear after 10 to 12 years after the onset of diabetes, because of diabetic endothelial and neural damage associated with persistent high serum glucose levels [43].

The WHO Global Report on Diabetes states that the number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014 and that the global prevalence among adults has risen from 4.7% to 8.5% over the same period. The overall prevalence of erectile dysfunction in diabetes is 59.1%, but significantly different across countries, South America 74.6%, Oceania and Africa 71.3%, and lowest amongst North American studies with 34.5% . Diabetic male patients generally have a greater prevalence and an earlier onset of erectile dysfunction than men without diabetes and it appears 10–15 years earlier in diabetic than in nondiabetic men. Erectile dysfunction in diabetics is directly associated with poor glycemic control as well as greater duration and severity of diabetes [44]. Moreover, it has been demonstrated that ED is an early sign of cardiovascular events, particularly coronary heart disease. Prevention of cardiovascular disease through screening and management of cardiovascular risk factors in men with ED is very important [45].

Pathophysiology

The aetiology of ED in diabetes is considered to be multifactorial, pathophysiologic changes associated with diabetes can broadly be classified as vasculopathy, neuropathy, hypogonadism, and local pathological factors.

Men with erectile dysfunction that have macrovascular disease have diminished vasodilating responses causing less relaxation of the vascular smooth muscle tissue because of changes in the vessel that predispose to subsequent atherosclerosis, plaque formation, thrombosis leading to occlusive macrovascular disease, and microvascular disease due to deficient production of nitrate oxide in nonadrenergic noncholinergic neurons and in the endothelium [46]. These

abnormalities are associated with important accumulation of advanced glycation products, altered expression of arginase, a competitor of the NO synthase for its substrate L-arginine [47, 48]. All of these abnormalities cause a tendency toward vasoconstriction, such as that caused by phenilephrine and endothelin-1, resulting in lack of vasodilatation and inadequate penile erection.

Numerous mechanisms play important roles in the pathophysiology of erectile dysfunction in diabetic males, one of them is the polyol pathway, which forms sorbitol by action of the enzyme aldose reductase. Sorbitol accumulates inside the cells, causing diminished myo-inositol levels (a precursor of the phosphatidylinositol), required for the adequate functioning of the Na-K ATPase pump. Increased sorbitol concentrations additionally produce progressive peripheral nerve damage [49].

Regarding vascular component, endothelial damage is a central issue in ED, because in comparison with healthy males, diabetic male patients have a diminished arterial inflow, which has been observed microscopically with reduced diameter and deficient morphology of the vascular wall [50]. Contraction of cavernosal smooth muscle cells is also affected by hyperglycemia, which results in an increased forced response to vasoconstrictors. This could be partially explained because of sensitization in protein kinase C and Rho A-Rho kinase Ca^{2+} pathways, which may cause a tendency toward a flaccid stage and modify the responses to NO [51]. All of these mechanisms are further compromised by other factors that impact erectile function including apoptosis or atrophy of the cavernous smooth muscle, due to diminished expression of blc2, intracellular release of Ca^{2+}, increased connective tissue proliferation due to tumor growth factor beta causing fibrosis, and a deficient response to NO in the cavernous and sinusoidal artery, with a decrease in neuronal and endothelial levels of NO synthetase. In brief, there are several components that take place in the endothelial and neural damage in the periphery and central nervous system, which globally impact on ED in patients with DM.

Diabetes is associated with peripheral and autonomic neuropathy and both of these can contribute to ED. The mechanism for ED is due to the reduced or absent parasympathetic activity needed for relaxation of the smooth muscle of the corpus cavernosum, which is produced by the decrease of norepinephrine levels as well as an increase in acectylcholine, resulting in increased NO synthase (NOS) activity, which releases NO.

Other factor is Hypogonadism, associated with type 2 diabetes. One study reported that 20% of diabetic men with ED had frank hypogonadism with a total testosterone level below 8 nmol/L and 31% had borderline low total testosterone levels between 8 and 12 nmol/L. The mechanism of hypogonadism in diabetes is incompletely understood. Hypogonadism is also associated with obesity and advancing age, common factors in type 2 diabetes.

Diagnosis

The International Questionnaire for Erectile Function helps to determine the degree of erectile dysfunction and evaluate the progression or response to medical treatment, one of the questionnaires is the International Index of Erectile Function (IIEF) and its short form, IIEF5 (also known as SHIM: Sexual Health Inventory for Men). The erectile function domain of IIEF and SHIM has been validated to assess the presence and the severity grade of ED. In the erectile function domain of IIEF, men scoring ≤25 are classified as having ED and those scoring >25 are considered not to have ED, with a sensitivity of 97% and specificity of 88%. The SHIM scale, those who score ≤ 21 are considered to have ED and those scoring >21 are considered not to have ED and sensitivity 98% and specificity of 88%.

In certain cases, in which a more precise evaluation of vascular flows is needed, an echo Doppler could be performed to determine cavernous artery flux and morphology. In selected cases, other studies to determine the degree of damage of myelinated pudendal somatosensory fibers and unmyelinated fibers can be done. Additional studies include assessment of nocturnal penile tumescence and electrostimulation. Most of these studies, however, are more commonly used in research protocols than in everyday clinical practice [52].

Treatment

Approximately 20% of patients with ED received pharmacological treatment, for that reason, clinicians should broadly evaluate sexuality among DM patients, trying to improve the sexual activity of patients and consequently their quality of life [40]. Glycemic control is an important factor, a decrease in or maintenance of hemoglobin A1c below 7.0% were significantly associated with a change on IIEF-5.

The first line of treatment are oral medications (phosphodiesterase 5 inhibitors), followed by intracavernosal injection (alprostadil), and finally penile prosthesis.

The daily use of phosphodiesterase 5 inhibitors can improve not only sexual function but also diminishes urinary tract symptoms associated with prostate enlargement. Meta-analysis has confirmed that phosphodiesterase 5 inhibitors are effective treatments of ED in patients with diabetes [53].

Sildenafil citrate, tadalafil, udenafil, and vardenafil hydrochloride are the oral agents for the treatment of erectile dysfunction. All PDE5 inhibitors are less efficacious in

diabetic men. They all share the same mechanism of action, which involves the hydrolysis of guanosine monophosphate to guanosine 5′-monophosphate, diminishing it, causing an increase in the relaxation of the cavernosal smooth muscle mediated by NO, increasing the blood flow into the corpus cavernosum, and causing penile erection [54]. Vardenafil and sildenafil are more effective on an empty stomach and start working after 30 min, with peak action at 1 h and a window of action of 4–6 h. Tadalafil has a long half life with a therapeutic window of 36–48 h, which may aid spontaneity.

Common side effects of phosphodiesterase 5 inhibitors are headache, dyspepsia, bluish eye sight, and facial flushing; lumbar musculoskeletal pain has been found in patients receiving tadalafil and mirodenafil [53]. Phosphodiesterase type 5 inhibitors are contraindicated in those who are on nitrates, because of the potential for a dramatic fall in blood pressure.

Vacuum erection devices cause blood flow to be directed into the penis, and when a satisfactory erection is obtained, a compressive device is applied at the base of the penis in order to prevent blood return and lose the erection. Side effects include cold penis due to noncirculating blood, loss or diminished sensation due to nerve compression, and the uncomfortable process to obtain the erection using the device [55]. External support devices that hold the flaccid penis to allow penetration have been designed, but the use of these instruments has not gained acceptance among patients and their partners.

Another medical option is intraurethral suppositories of prostaglandin E-1 which are injected into the urethra. In men with diabetes, their reported efficiency rate to achieve satisfactory intercourse is 60%, although in clinical practice, they have not proved to be as effective [56, 57]. Injections of prostaglandin E-1 directly into the corpus cavernosum have a direct effect on blood vessels, causing immediate penile erections, with a reported response rate above 83% [58]. Main limitations include the need of injection prior to the sexual encounter, its impact on the spontaneity of sexual intercourse, and adverse effects including penile pain, hematomas, infection, fibrosis and priapism, prolonged and painful erections [59].

Patients not responding to medical therapy, unsatisfied with side effects or patients who prefer a permanent solution should consider a penile prosthesis implant (PPI). PPI improves flaccidity and rigidity, male satisfaction and correlates positively with satisfaction of the sexual partner. The rate of complications related to penile implantation is lower than 5%; they may be catastrophic however and include misplacement, migration, perforation, and a low risk of infection (less than 1.8%) using antibiotic prophylaxis, antibiotic impregnation, or hydrophobic-coated prosthesis [60].

Urinary Tract Infections

Urinary tract infection (UTI) is the most common infection among patients with diabetes mellitus [7, 8], with estimates of diabetics suffering from UTI reaching 10% of patients visiting hospitals [61].

The worldwide prevalence of urinary tract infections (UTI) is around 150 million persons per year [62]. DM patients have a higher incidence of infections in general, and UTI are not the exception. In a cohort of over 6000 patients with diabetes mellitus enrolled into 10 clinical trials of diabetes therapies, the incidence of urinary infection was 91.5/1000 person/years for women and 28.2/11,000 for men. [63]. In the Dutch National Survey of General Practice, patients with Type 1 diabetes mellitus were1.96 times more likely to experience urinary infection and with Type 2 diabetes 1.24 times more likely. [64]. In a recent study of a cohort of 460 hospitalized participants, the overall prevalence of UTI was 27.39% among diabetic patients and 17.83% among nondiabetic participants, with a higher prevalence in ages between 40 and 49 and a higher prevalence between women (43%) in comparison with men (13.8%) [61]. The high prevalence of UTI recorded among the age group 40–49 years could be due to increased rate of sexual activity in this age group. Metabolic abnormalities and long-term complications including neuropathy and nephropathy are presumed to be determinants of increased infectious morbidity [65].

The variety of UTI patients with diabetes ranges from asymptomatic bacteriuria to cystitis, pyelonephritis, renal abscess, xantogranulomatouse pyelonephritis to severe urosepsis [66]. DM is also associated with severe cutaneous infections of the genitals such as Fournier's gangrene.

Asymptomatic bacteriuria is more prevalent in women, due to the anatomical length of the urethra, and it is closer to the warm, moist, vulvar, and perianal areas that are commonly colonized by enteric bacteria [66]. Asymptomatic bacteriuria occurs in 8–26% of diabetic women, a prevalence estimated to be 2–3 times higher than nondiabetic women [67].

DM female patients frequently suffer bacterial cystitis with higher prevalence of both asymptomatic bacteriuria and symptomatic UTI added to recurrent complications, compared to healthy women [62]. Bacterial cystitis is frequently suffered by diabetic patients; it is more common in women than in men, especially in those with type 2 DM. Diabetic women have a higher prevalence of asymptomatic bacteriuria than healthy women, and they have a greater tendency for developing symptomatic UTI and recurrent complications with higher incidence of more serious complications [68, 69]. For women with diabetes and asymptomatic bacteriuria, those with type 2 diabetes have an increased risk for pyelonephritis and subsequent impairment of renal function [68, 69].

Type 2 DM is more than a risk factor for community acquired UTI and is a high predisposition for healthcare associated UTI, such as catheter-associated UTI, postrenal transplant recurrent UTI, and catheter-associated UTI [66]. Hospitalization due to pyelonephritis occurs more frequently in diabetic patients, and they are at higher risk of developing acute pyelonephritis, which could progress to renal abscess, pyelitis or emphysematous cystitis or pyelonephritis, and bacteriemia [66, 70]. In a Canadian report, diabetic women were 6–15 times more frequently hospitalized for acute pyelonephritis and diabetic men 3.4–17 times [71].

A retrospective analysis found that diabetes mellitus was one of four variables independently associated with a poor outcome (clinical or bacteriological failure or relapse) of therapy for acute pyelonephritis. Other evidence supporting increased severity of infection is an increased frequency of bacteremia, more prolonged duration of fever, and increased mortality (12.5% with diabetes and 2.5% without) in older patients with diabetes. Over 90% of episodes of emphysematous pyelonephritis cases occur in persons with diabetes and 67% of episodes of emphysematous csystitis [72]. Other clinical manifestations that are unique or strongly associated with diabetes include abscess formation and renal papillary necrosis.

Pathophysiology

The development of UTI in women is preceded by colonization of the vaginal and periurethral epithelium by the infecting organism. Ascension to the bladder may then ensue E. coli causes the overwhelming majority of UTIs. Normal host defense mechanisms usually prevent entry to or persistence of bacteria within the urinary tract. The growth rate of bacteria and fungi in urine is stimulated by glycosuria [73]. In addition, higher renal parenchymal glucose levels create a favorable atmosphere for multiplication of many microorganisms [66]. A reduction of urinary Tamm Horsfall glycoprotein (THP) excretion which correlates with reduction of renal mass is consistently observed in diabetic nephropathy. Glycation of THP in patients with diabetes or renal diseases also reduces the capacity of THP to inhibit bacterial adherence to human uroepithelium [74].

Bacterial attachment to the uroepithelium is the necessary initiating event permitting bacterial persistence. Uropathogenic *E. coli* are specialized for success in the urinary tract, elaborating virulence determinants such as adhesins (type 1, P and S fimbriae, and afimbrial adhesin), which bind to specific molecules in the uroepithelium, such as glycosphingolipids and uroplakins [75]. A recent study examined the ability of three representative clinical isolates of uropathogenic *E. coli* to adhere to uroepithelial cells collected from urine of women with and without diabetes. Uropathogenic *E. coli* expressing type 1 fimbriae were twice as adherent to cells from women with diabetes as compared with cells collected from the women without diabetes.

Local urinary cytokines regulate host defence against urinary tract infections. DM results in abnormalities in the host immune defense system that may result in higher risk of developing infection. Immunologic impairments such as defective migration and phagocytes alterations of chemotaxis in polymorphonuclear leukocytes are common in DM patients [76]. A potential risk factor for urinary tract infection is polymorphonuclear leukocyte dysfunction in a high-glucose state. Significantly lower urinary IL-8- and Il-6-concentrations are found in diabetic women compared with nondiabetic controls, and these lower levels correlate with lower urinary leukocyte counts [68, 69]. One recent study shows that monocytes from women with type 1 diabetes produced lower amounts of proinflammatory cytokines upon stimulation with lipolysaccharide, women with diabetes who developed bacteriuria also produced lower urinary IL-6 concentrations, as compared with specimens from bacteriuric control subjects without diabetes [68, 69]. Diminished neutrophil responses, lower levels of cytokines and leukocytes facilitate adhesion of microorganisms to uroepithelial cells and the development of infections [77].

General host factors associated with risk of infection in patients with diabetes include age, metabolic control, duration of diabetes mellitus, microvascular complications, urinary incontinence, and cerebrovascular disease or dementia. The only risk factor associated with acute cistitis in premenopausal women with Type 1 diabetes was sexual activity. Previously suggested as possible risk factors, duration of diabetes or elevated HBA1c levels have not been shown to increase the risk of urinary tract infections in recent studies [68, 69].

The increased frequency of UTI in patients with diabetes might be associated to nerve damage caused by hyperglycemia, affecting the capacity of bladder to sense the presence of urine and leading to stagnation of urine for a long time, or inadequate bladder emptying due to ineffective detrusor contraction, increasing the probability of infections [62]. Over 50% of men and women with diabetes have bladder dysfunction which may impair voiding and facilitate infection. Urinary incontinence is consistently associated with urinary tract infection in diabetic women, but this association is not likely causative. Bladder dysfunction occurs in 26–86% of diabetic women depending on age, extent of neuropathy, and duration of diabetic disease. The possibility that voiding disorders are contributing to UTI should be considered in all diabetic patients.

Also of importance is the fact that many diabetic patients are infected with non-Escherichia coli species, in particular Klebsiella, other gram-negative rods, enterococci, and group B streptococci. Additionally, urinary infections with Candida

Albicans occur commonly in diabetic women but infrequently in other women.

Clinical Manifestations

UTI in DM patients can be the origin of severe complications that can end up in sepsis, organ failure, and death. Therefore, it is important to be vigilant of the usual clinical manifestations such as urinary urgency, frequency, bad urine odor, pain, dysuria, tenesmus, incomplete emptying and incontinence for lower UTI; and costovertebral angle pain or tenderness, fever, chills for upper UTI [66]. Diabetic patients generally present with symptoms similar to nondiabetic patients, but clinical signs may be altered in some patients with peripheral or autonomic neuropathy. Patients with diabetes are more likely to have more severe presentations of pyelonephritis including fever bacteremia and bilateral renal involvement. Less frequent presentations of urinary infection which occur most often in patients with diabetes include emphysematous cystitis or pyelonephritis, ureteral obstruction secondary to papillary necrosis, and renal or perinephric abscesses.

Diagnosis

Frequent and early screening for UTI should be performed in DM patients with suggestive symptoms, in order to establish the appropriate early treatment and to avoid complications.

As soon as the clinical diagnosis of UTI is suspected, a midstream urine sample must be examined, looking for the presence of leukocytes (more than 10 leukocytes/mm^3) or a positive dipstick leukocyte esterase test to detect pyuria. Microscopic or macroscopic hematuria is sometimes observed [66] associated to positive nitrites and the presence of bacteriuria. A urine specimen for culture should be obtained prior to initiating antimicrobial therapy for every diabetic patient presenting with pyelonephritis or complicated urinary tract infection. Women with symptoms consistent with acute cystitis and who do not have diabetic nephropathy or other long-term complications, particularly if they have a prior history of recurrent acute cystitis, do not usually require a urine culture. However, these women should also have a urine specimen for culture if this is a recurrent episode within 1 month of treatment, if empiric therapy has failed, or if there has been recent antimicrobial treatment so resistant organisms are more likely.

Pyuria is a universal accompaniment of symptomatic urinary tract infection. Thus, the presence of pyuria, by itself, is not useful for diagnosis of urinary tract infection or to differentiate asymptomatic and symptomatic infection. The absence of pyuria, however, is useful to exclude urinary tract infection in patients with questionable symptoms.

A diagnosis of bacteriuria is made when >105 cfu/ml of an organism is isolated from a voided urine specimen. Despite the fact that Escherichia coli is the most frequent bacteria in patients with urinary tract infections, unusual, multidrug resistant and aggressive pathogens are more prevalent in DM patients, including Klebsiella, gram negative rods, enterococci, group B streptococci, Pseudomonas and Proteus mirabilis [78]. Type 2 DM is a risk factor for fungal UTI, such as candida, these patients are more predisposed to be infected by resistant pathogens, including extended-spectrum β-lactamase-positive Enterobacteriaceae, fluoroquinolone-resistant Uropathogens, carbapenem-resistant Enterobacteriaceae, and vancomycin-resistant Enterococci [66].

The increased frequency of serious complications of urinary tract infection in patients with diabetes requires a low threshold for obtaining diagnostic imaging. Ultrasound scanning is safer, less costly, and easier to perform. These methods allowed detection of calculi, obstruction, and incomplete bladder emptying. Computerized tomography (CT) is now accepted as the most sensitive imaging modality for diagnosis and follow-up of abnormalities potentially associated with urinary tract infections. An enhanced CT scan is preferred, but contrast media should be used with caution in patients with diabetes mellitus or with renal disease.

Treatment

Treatment of urinary tract infection in patients with diabetes is generally similar to nondiabetic patients. Key factors to consider include whether the patient is asymptomatic or symptomatic, whether infection is localized to the bladder or kidney, and renal function. Glycemic control is helpful in the control of (UTI) [62].

Assuming that asymptomatic bacteriuria is more common and that the consequences more deleterious among women with diabetes, the question as to whether to attempt to eradicate it is of considerable relevance. In a randomized controlled trial of type 1 and type 2 diabetic women with asymptomatic bacteriuria, women were randomized to treatment with antimicrobials or no treatment for episodes of asymptomatic bacteriuria >3 years. Importantly, the study demonstrated that screening and treatment episodes of asymptomatic bacteriuria had no impact on overall occurrence of symptomatic urinary tract infections or hospitalizations [79]. Therefore there are no short- or long-term benefits for treatment of asymptomatic bacteriuria in women with diabetes mellitus. Asymptomatic bacteriuria by itself is not associated with an increased rate of progression to renal impairment or other long-term complications in patients with diabetes [80].

Acute cystitis in women with good glucose control and without long-term complications should be managed as uncomplicated urinary infection, usually with short-term antimicrobial therapy [81]. However, patients with pyelonephritis and severe systemic symptoms including nausea and vomiting or hemodynamic instability should be hospitalized for initial parenteral antibiotic therapy.

The choice of initial empiric antimicrobial therapy should consider current treatment guidelines, the patient's metabolic status and tolerance, the clinical presentation, and known or suspected local or institutional susceptibility of uropathogens (Table 59.1). The use of trimethoprim, cotrimoxazole, or nitrofurantoin is considered as the standard regimen of antibiotic therapy [82]. Broad spectrum cephalosporins and fluoroquinolones are the drugs of choice for pyelonephritis. However, alternate regimens such as the carbapenems meropenem, ertapenem or doripenem or betalactam/beta lactamase inhibitors such as piperacillin/ tazobactam or ampicillin/sulbactam may be appropriate if antimicrobial resistance is a concern. For patients who present with severe sepsis or septic shock, broad spectrum antimicrobial therapy to provide maximal coverage for resistant organisms should be initiated pending urine culture results. Antimicrobials with nephrotoxic side effects, e.g., aminoglycosides should be used with caution in patients with renal insufficiency. Nitrofurantoin should be avoided in renal failure as drug metabolites accumulate and may cause peripheral neuropathy [83]. There are studies reporting higher frequency of extended spectrum beta-lactamase producing E. coli and Klebsiella pneumonia in diabetic patients. However, these studies didn't report whether diabetes was an independent risk factor for increased resistance [84].

Table 59.1 Recommendations for antimicrobial therapy in uncomplicated cystitis in patients with diabetes mellitus

Antimicrobial	Regimen	Duration
First-line		
Fosfoycin trometamol	3000 mg	Single dose
Nitrofurantoin	50–100 mg orally 3–4 times a day	5 days
Nitrofurantoin monohydrate/ macrocrystals	100 mg twice a day	5 days
Trimethoprim/ sulfamethoxasole	800/160 mg orally every 12 h	3 days
Alternatives		
Ciprofloxacin	250–500 mg orally every 12 h	3 days
Levofloxacin	250–500 mg every 12 h	3 days
Norfloxacin	400 mg orally every 12 h	3 days
Ofloxacin	200 mg orally every 12 h	3 days
Cephalexin	500 mg 4 times daily	7 days
Axetil cefuroxime	500 mg twice daily	7 days
Cefpodoxime proxetil	100 mg orally every 12 h	3 days
Cefixime	400 mg daily	3 days

Among women with type 1 diabetes, sexual activity has been identified as the most important risk factor for the development of urinary tract infections, similar to women without diabetes. Continuous or postcoital prophylaxis with low-dose antimicrobial agents and intermittent self-treatment with antimicrobials are the recommended strategies to prevent recurrent urinary tract infections in women without diabetes which also could be useful in women with diabetes [85].

Recurrent infection in young women without long-term complications of diabetes is managed as acute uncomplicated cystitis, including antimicrobial therapy given as long-term low dose or post intercourse prophylaxis for women with very frequent recurrence. For patients with complicated infection, it is essential to identify and correct any known urologic abnormalities and to optimize voiding, including use of intermittent catheterization where appropriate.

Conclusions

Patients with diabetes are highly susceptible to urologic complications. They may be serious, life threatening, and affect quality of life. The underlying mechanisms determining the increased risk and severity of infection are not fully described, but alterations in specific components of the host response, metabolic abnormalities, and long-term complications of diabetes likely contribute. It is important to take into account these comorbidities in the management of diabetes and to understand their pathogenesis to prevent systemic dissemination. Many patients with diabetes accept these comorbidities are part of their disease but clinicians should be aware, interrogate, and screen for these complications in order to indicate the adequate treatment. Controlled clinical trials of therapy comparing patients with and without diabetes mellitus or diabetic patients stratified by adequacy of control and complications will be necessary to improve management of this common and important problem.

Multiple Choice Questions

1. Urologic complications in people with diabetes are associated to:
   (a) Nerve function disturbances
   (b) Loss of innervations of neuromuscular terminals
   (c) Abnormal immune responses
   (d) Altered sympathetic/parasympathetic innervations
   (e) **All of the above**
2. Peripheral accumulations of fat in the abdominal region of DM patients have been associated to an increased risk of urologic complications including:

(a) **Urinary incontinence**
(b) **Erectile dysfunction**
(c) **Benign prostatic hyperplasia**
(d) **Urinary tract infections**
(e) **Cancer**

3. Diabetic cystopathy is characterized by:
(a) **Urinary incontinence**
(b) **Increased post voiding residual volume**
(c) **Urinary tract infection**
(d) All of the above
(e) None of the above

4. Bladder symptoms of diabetic cystopathy include:
(a) **Polyakiuria**
(b) Decreasing caliber and strength of the voiding flow
(c) Terminal dribbling
(d) **Urgency incontinence**
(e) High postvoid residual urine

5. Infiltration of the detrusor muscle can be achieved with:
(a) Oxybutynin
(b) Solifenacin
(c) **Botulinum toxin**
(d) Darifenacin
(e) Tolterodine

6. Positive predictive predictors of benign prostatic hyperplasia:
(a) Urinary tract infection
(b) Plasma insulin levels
(c) Dysuria
(d) **Urinary urgency**
(e) Fasting blood glucose

7. Patients with benign prostatic hypertrophy and enlarged prostate should be treated with:
(a) Nonselective alpha-1 blockers
(b) Selective alpha-1 blockers
(c) Alpha reductase inhibitors
(d) **Alpha-1 blockers combined with 5 alpha reductase inhibitors**
(e) Surgical management is the only option

8. The reported prevalence of sexual dysfunction in men with type 2 diabetes:
(a) 18%
(b) 37%
(c) **46%**
(d) 53%
(e) 71%

9. The reported prevalence of sexual dysfunction in women with type 1 diabetes:
(a) 18%
(b) 37%
(c) 46%
(d) 53%
(e) **71%**

10. Erectile dysfunction:
(a) is a minor complaint of men with diabetes
(b) has not been quantified
(c) is usually present at diagnosis
(d) **is the third most common chronic complication and the most significantly affecting quality of life**
(e) is common but less relevant regarding quality of life

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Musculoskeletal Complications of Diabetes Mellitus

60

Deep Dutta, Rajiv Singla, Meha Sharma, Aarti Sharma, and Sanjay Kalra

Introduction

Musculoskeletal complications of diabetes are a diverse set of disorders which are associated with significant impairment of the quality of life in affected patients. Lack of awareness amongst patients and also perhaps amongst the caregivers contributes to increased morbidity due to this complications amongst patient with diabetes.

In contrast to the extensively studied microvascular and macrovascular complications of DM, data and evidence on the musculoskeletal complications of Diabetes Mellitus (DM) is largely derived from observational studies. Pathogenic mechanisms for many of these conditions are yet to be fully elucidated. An important aspect of the musculoskeletal complication of DM is that their occurrence is not limited to individuals with diabetes. Such conditions are also known to occur in a diverse set of non-diabetes disorders. The only exception to this rule is perhaps the diabetic muscle infarction (DMI)/ myonecrosis, which is believed to occur exclusively amongst patients with DM [1].

In a study from Kerala, the prevalence of rheumatologic and musculoskeletal disorders was observed to be very common in patients with diabetes having a prevalence of 42.58% in a cohort of 310 individuals. With the exponential increase in the burden of diabetes, especially in India, the burden of patients with musculoskeletal complication of diabetes is also going to increase manifold. Some of the unique challenges with type-2 diabetes in India is the nearly two decade earlier onset in Indians as compared to rest of the globe, a greater insulin resistance, systemic inflammation, a more severe beta cell impairment, greater central adiposity, increased body fat percentage, and a more rapid progression from prediabetes to diabetes [2]. Duration as well as severity of diabetes has been often linked with increased occurrence and severity of the musculo-skeletal complication of diabetes. In this chapter, a review of the major musculoskeletal complications of diabetes has been done, highlighting their pathophysiology, treatment modalities, and outcomes (Table 60.1).

Musculoskeletal manifestations can be divided largely into three categories:

- Bone effects of diabetes
- Muscle effects of diabetes
- Joint and connective tissue effects of diabetes

Table 60.1 Musculoskeletal involvement in diabetes mellitus

Conditions occurring more frequently in DM
• Shoulder capsulitis
• Limited joint mobility
• Dupuytren's disease
• Stenosing flexor tenosynovitis (trigger finger)
• Neuropathic charcot arthropathy
• Calcific shoulder periarthritis
• Carpal tunnel syndrome
Conditions unique to DM
• Diabetic muscle infarction
Condition sharing risk factors of DM and metabolic syndrome
• Diffuse idiopathic skeletal hyperostosis
• Crystal-induced arthritis
• Osteoarthritis
Miscellaneous
• Bone health and osteoporosis

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Bone Effects of Diabetes: Bone Density and Fracture Risk

Effect of diabetes on bone health is quite complex and interesting. Effect varies with type of diabetes and with site of skeletal system. Both type 1 and type 2 diabetes are associated with poor bone health and increased fracture rate, but their effect on bone mineral density varies. Type 1 diabetes is associated with decreased bone density in majority of studies done. Uncontrolled type 1 diabetes may, in fact, prevent an adolescent from acquiring peak bone mass. When assessed in midlife, most of the studies show, bone mineral density to be decreased. Low body mass index, lower lean mass contributes to lower BMD in patients with T1DM. Different studies have consistently shown that fracture risk is increased by around two times, at lumber spine, hip, and distal radius in patients with type-1 diabetes. Major pathophysiologic factor responsible for decreased bone density in type 1 diabetes is lack of insulin that, otherwise, acts as an anabolic agent for bone. Raised blood glucose in uncontrolled diabetes also deteriorates bone quality by formation of non-enzymic glycated collagen cross-links which are much weaker than, usually formed, enzymic pyrilodine cross-links. Another important factor predisposing to poor bone health in this population is low body mass index. Only measure, which is effective, for prevention and recovery is adequate glycaemic control as that would signify normal blood glucose levels with optimum insulin therapy [3].

Situation in type 2 diabetes is much more complex as these patients often have associated hyperinsulinism. Bone mineral density in type 2 diabetes can vary from low to normal to some patients even increased, depending on the disease state and the clinical scenario. Raised BMI in obese type-2 DM patients has a trophic effect on BMD. However, it must be highlighted that even in patients with normal to increased BMI in T2DM, the fracture rates has been consistently demonstrated to be increased in T2DM. This can be attributed to the poor bone quality in such patients, secondary to glycation of bone matrix secondary to persistent hyperglycaemia in patients with T2DM. The authors have observed in a cohort of type-2 diabetes patients that is the lean mass, which has the maximum impact on bone health in diabetes. A greater lean mass leads to a greater dynamic loading of the bones, which has a trophic effect on bone health and density. Sarcopenia due to any cause is associated with low bone density in diabetes.

Apart from weakening the bone, accumulation of advanced glycosylation end-products (AGEs) in the organic bone matrix by nonenzymatic glycation interfere with normal osteoblast development, function, and attachment to the collagen matrix. In type 2 diabetes, differential effect at trabecular and cortical sites has also been noted with preservation of trabecular bone and loss of cortical bone mass. There are clinical studies which show that in T2DM, most of the fractures occur at sites that are rich in cortical bone. Risk factors other than bone density also need to be kept in mind in patients with diabetes, most notable being microvascular complication (esp. neuropathy and retinopathy), macrovascular complications, and muscle weakness.

Smoking, use of glucocorticoids, associated inflammatory diseases like inflammatory arthropathy all are associated with poorer bone mineral density and bone health in diabetes. Bone health is often a neglected aspect of diabetes management. It would a good clinical practice from the clinician's point of view to avoid medications which are associated with impaired bone health in patients of diabetes with established low bone mineral density. Pioglitazone and SGLT2 inhibitors have been linked to adverse bone mineral outcomes in diabetes. Pioglitazone (thiazolidinediones) inhibits bone formation directly, by diverting mesenchymal stem cell precursors from the osteoblast to the adipocyte lineage. SGLT2 inhibitors use has been linked to increased phosphate reabsorption from the kidneys. Increased phosphate reabsorption and increased circulating phosphorous leads to secondary hyperparathyroidism, increased circulating levels of phosphatonins, all of which have an adverse impact on bone mineral density. The high prevalence of vitamin-D deficiency also contributes to impaired bone mineral health and peak bone mass in adulthood.

Muscle Effects of Diabetes

Muscles are a major user of insulin-mediated glucose uptake. In face of insulin resistance in type 2, proteomics studies have revealed weakened metabolic flexibility, i.e. difficulty in switching between glucose metabolism and fatty acid utilization with preferential oxidative-to-glycolytic shift. There is altered mitochondrial function, reduced lipid oxidation, increased cellular stress response, and enhanced detoxification mechanisms. All these metabolic change result in changes in contractile proteins and altered cytoskeletal proteins and also fatigue and tiredness.

Acute and chronic neuropathies associated with diabetes can lead to muscle atrophy and weakness. For example, carpal tunnel syndrome (discussed in sections ahead) can lead to atrophy of hand muscles, and distal polyneuropathy can lead to loss of small muscles of foot. Primary diseases of muscles seen in diabetics include diabetic myonecrosis and amyotrophy.

Diabetic Myonecrosis

Spontaneous infarction of muscle in diabetic patients is a rare but well-known entity. Approximately 200 cases have been reported in literature so far. The pathophysiology for diabetic myonecrosis has not been fully elucidated, but it is proposed to be ischemic in nature without any obvious athero-embolism or vascular occlusion of any major artery. It is more commonly seen in patients who are dependent on insulin and already have underlying microvascular complications.

Clinically, the disease has slight male preponderance and patient usually present with a disabling and constant pain involving quadriceps muscles. Other areas which can be involved in minority of cases include calf muscles, upper limb, and neck muscles. There may be an apparent swelling at site of involvement. Asymmetry is a hallmark of this disease. Bilateral involvement occurs in one-third of patients. Blood investigation reveals raised levels of ESR and CRP, while creatine kinase may be raised or normal during early or late stage of presentation, respectively. Leucocyte count and temperature are normal and helps in differentiation from infective pathology. Sonography reveals diffuse or focal muscle edema and is invaluable in ruling out deep vein thrombosis or major arterial thrombosis. Magnetic resonance imaging is investigation of choice in such cases and the involved muscle shows hyperintensity on T2-weighted sequences and addition of contrast differentiates non-enhancing infarcted muscle from surrounding inflammation or edema. Additional findings on MRI can be subcutaneous edema, subfascial fluid, and loss of the normal fatty intramuscular septa. Biopsy is not generally indicated, but reveals muscle edema and infarction along with evidence of microangiopathy.

Disease generally resolves on its own by 6–12 weeks. Rest and pain relief are mainstay of therapy. But as there is evidence of microangiopathy and association with other microvascular complications, antiplatelets are generally advised. Constant vigil, however, is required as some of the cases can be complicated by compartment syndrome. Moreover, recurrence rate is very high and half of the cases would have recurrence. The mean mortality rate associated with DMI is 10% within 2 years of initial diagnosis, predominantly as a result of macrovascular complications.

Diabetic Amyotrophy

Amyotrophy or diabetic lumbosacral plexopathy has overlapping clinical presentation with diabetic myonecrosis. But, amyotrophy occurs predominantly in type 2 patients who are fairly controlled or has recently been diagnosed. It also present with acute onset proximal leg pain followed by muscle weakness. Disease is usually unilateral at onset, but bilateral involvement eventually occurs in majority of patients. About one-third of patients may have distal onset of disease. This condition is also associated with distal and proximal sensory loss. New onset autonomic symptoms may occur in up to half of the patients and more than 80% patients would report loss of at least 10% body weight. Rarely, muscles of upper limb and thorax can be involved.

Underlying pathophysiology is not clear (e.g., ischemic, metabolic and/or inflammatory), though there is general consensus that ischemic injury due to non-systemic microvasculitis is most likely cause. Electrodiagnostic studies, in presence of typical features, are sufficient to clinch the diagnosis. Abnormalities are localized to lumbosacral plexus and peripheral nerves of lower limb. HIV and cytomegalovirus can cause similar disease with same electrodiagnostic findings. Inflammatory myopathies such as polymyositis and dermatomyositis should always be ruled out. Associated classical cutaneous manifestations makes easy for dermatomyositis to be ruled out. Polymyositis is classically associated with elevated levels of creatine-phosphokinase (CPK) in the blood which is not seen in amyotrophy.

Disease usually runs a self-limited course with spontaneous resolution but some residual problem remains in large majority in form of either weakness or persistent pain. Course of disease can run over months. Treatment is only symptomatic. No evidence exists to favour treatment with steroids, immunosuppressants, or immunoglobulins.

Joint and Connective Tissue Effects of Diabetes

Joint and connective tissue diseases are more common in people with diabetes (Table 60.2). There is no single mechanism that has been shown to account for the development of joint and connective tissue effects of diabetes, viz. limited joint mobility (LJM), shoulder adhesive capsulitis, stenosing flexor tenosynovitis, and Dupuytren's contracture amongst

Table 60.2 Prevalence of joint and connective tissue diseases in people with and without diabetes

Musculoskeletal disorder	With diabetes (%)	Without diabetes (%)
Shoulder capsulitis	11–30	2–10
Limited joint mobility	8–50	0–26
Dupuytren's disease	20–63	5–10
Carpal tunnel syndrome	11–16	2–5
Stenosing flexor tenosynovitis	10–12	<1
Diffuse idiopathic skeletal hyperostosis	13–50	2–15

others. However, the shared cause of these conditions seems to involve abnormal connective tissue deposition around joints, in tendon sheaths, and in the palmar fascia, respectively.

Accumulation of advanced glycation end products (AGEs) with cross-linking of collagen and other macromolecules has been proposed as a potential pathogenetic mechanism. It is likely that poorer glycaemic control over time with resulting AGE formation influences the development of hand and shoulder problems amongst patients with DM.

Adhesive Capsulitis of the Shoulder (Frozen Shoulder Syndrome, Shoulder Periarthritis) Enter Box 60.1

Box 60.1 Adhesive Capsulitis of Shoulder

Painful progressive restriction of shoulder motion
30 months: Average duration of symptoms
10–29% prevalence amongst diabetics
Treatment: Analgesics, physiotherapy, intra-articular corticosteroid injection, arthroscopic capsular release

The prevalence of adhesive capsulitis is 11–29% in patients with T2DM, as compared to only 2–3% in healthy euglycaemic individuals. Risk factors for adhesive capsulitis include older age, increased duration of diabetes, history of myocardial infarction, presence of peripheral neuropathy and nephropathy. Adhesive capsulitis usually presents as painful progressive restriction of range of shoulder movement, especially on abduction and external rotation. Its natural history can be divided into three phases: pain, stiffness, and recovery. The length of the recovery phase depends on the duration of the stiffness phase, with symptoms lasting for an average of 30 months. Adhesive capsulitis can involve any of the large joints in diabetes. Frozen shoulder syndrome is perhaps the most common type of adhesive capsulitis (Table 60.2). Shoulder adhesive capsulitis is more likely to develop in older individuals with either type of DM and in those with longer duration of disease amongst patients with type 1 DM, history of myocardial infarction, associated nephropathy, and/or neuropathy [4].

Analgesics physical therapy and intra-articular corticosteroid injection are first-line therapy during the initial painful phase of shoulder adhesive capsulitis. Intra-articular injection, early in the course of the disease, has been linked to improved outcomes and better mobility in the long run. It must be highlighted that oral corticosteroids have limited role and should be routinely used in patients with adhesive capsulitis. Oral glucocorticoids are not associated with improved mobility outcomes in the long run and additionally they adversely affect glycaemic control. Intensive physiotherapy including stretching and mobilization also has a key role in improving clinical outcomes. Arthroscopic capsular release has been an effective treatment modality for refractory shoulder adhesive capsulitis in a few patients. Radiographic-guided hydro-dilation and manipulation under anesthesia have been tried in refractory patients with mixed long-term outcomes.

Limited Joint Mobility (Diabetic Cheiro-Arthropathy) Enter Box 60.2

Box 60.2 Limited Joint Mobility

Collagen disease seen only in diabetes
Prevalence 8–50%
Stiff hands with thick, tight, and waxy skin
Asymptomatic
Harbinger of microvascular disease

Limited joint mobility (LJM) also known as ‘diabetic cheiro-arthropathy’ is characterized by stiff hands. The skin is markedly thick, tight, and waxy especially on the dorsal aspects of the hands which are usually, symmetrically affected: mimicking scleroderma.

Patients with LJM have limited extension of the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints, usually beginning in the ulnar digits and spreading radially. Screening for LJM can be done by physical examination. The prayer (preachers) sign involves the patient holding the hands opposed to one another vertically with elbows flexed and wrists extended. A positive sign is observed by an inability of the patient to completely approximate the palmar surface of the digits.

In the table top sign, the patient places the palms flat on a hard surface with the digits spread. Normally, the entire palmar surface of the digits should contact the table. If the test is positive, the digits and palm will not lie flat. Both these tests can also be positive with Dupuytren’s contracture. The prayer sign is also useful for staging of LJM as follows:

Stage 0: normal findings on prayer sign examination.
Stage 1: involvement of one or two interphalangeal joints bilaterally.
Stage 2: Inability to approximate three or more interphalangeal joints bilaterally.
Stage 3: Hand deformity at rest.

The prevalence of LJM in diabetes varies from 8% to 50%. The frequency of LJM in diabetics increases with

increasing diabetes duration. The importance of LJM can be highlighted by the fact that its presence is an indicator for other associated more grave microvascular and macrovascular complications of diabetes. An association with microvascular complications (retinopathy, microalbuminuria) has been shown, both in Type 1 and in Type 2 diabetes. LJM increases the risk for microvascular disease in Type 1 diabetes. There is an 83% risk for microvascular complications after 16 years of diabetes in the presence of LJM, compared with a 25% risk in the absence of LJM. Patients with LJM may be at higher risk for foot ulceration because of concomitant limited joint mobility at the hallux.

Treatment of LJM is not very satisfactory. Physiotherapy to increase the range of motion in the hand joints is fundamental. This involves active and passive mobilization and use of corrective splints. Glucocorticoids injection of flexor tendon sheaths leads to resolution of finger contractures in every two out of three patients with LJM. At a more practical level, optimization of glycaemic control is believed to be vital for the management of LJM.

Dupuytren Contracture (DD)

DD is a progressive fibro-proliferative disorder resulting in abnormal scar-like tissue in the palmar fascia leading to irreversible, permanent, painless, and progressive contracture of the involved digits. DD is commonly bilateral, and 'Dupuytren-like' fibrotic tissue can occur on the dorsum of the hand over the knuckles (Garrod's pads), feet (Lederhose's disease), and penis (Peyronie's disease). The ring finger is the most frequently involved, followed by the little finger, and then middle finger; the index finger and thumb are rarely involved.

The incidence of DD also increases with concurrent patient clinical conditions or factors such as diabetes, smoking, chronic alcoholism, seizures, and infection. Microvascular changes in smokers may play a role. Hand examination also reveals palpable palmar nodule or nodules.

The prevalence of DC in diabetes ranges between 20% and 63%, considerably higher than amongst nondiabetic subjects (13%). DC in diabetic subjects is associated with diabetes duration, long-term poor metabolic control, and presence of microvascular complications. LJM and DC may coexist in the same patient [5].

DD must be distinguished from several other conditions that affect the hand, including trigger finger, stenosing tenosynovitis, a ganglion cyst, or a soft-tissue mass. Unlike DC, trigger finger typically involves pain with flexion followed by the inability to extend the affected digit. Stenosing tenosynovitis may be distinguished from DD by pain and a history of overuse or trauma. A small, movable nodule that is tender to palpation at the metacarpophalangeal joint is likely a ganglion cyst. Treatment of DC involves optimized glycaemic control and physiotherapy. Topical steroid injection and surgery are reserved for the more severe cases. Surgery yields satisfactory results.

Calciphylaxis

Calciphylaxis is a form of small vessel vasculitis. It has been reported in patients with renal failure as well as diabetes. Clinically, they present as small tender areas on the skin, initially red in color, which then become subcutaneous nodules, leading to poorly healing necrotizing skin ulcers. Key to treatment is to ensure a good glycaemic control and analgesics for pain relief.

Stenosing Flexor Tenosynovitis (Trigger Finger)

Stenosing flexor tenosynovitis typically presents with locking (or 'triggering') of fingers in flexion, extension, or both, most commonly involving the thumb, middle, and ring fingers. At clinical examination, locking is reproducible on active or passive finger flexion. Moreover, a nodule is palpable at the base of affected finger. The prevalence of stenosing flexor tenosynovitis ranges between 5% and 36% amongst patients with type 1 and 2 DM, as compared with 2% in the general population. Compared with nondiabetics, patients with DM are more likely to have multiple fingers involved simultaneously by stenosing flexor tenosynovitis [6].

In diabetic subjects, it is associated with diabetes duration, long-term poor metabolic control, and presence of microvascular complications. Additionally, it has been suggested as an indicator of glucose dysmetabolism that should prompt glucose measurement and oral glucose tolerance test in the general population. Treatment of stenosing flexor tenosynovitis includes modification of activities to avoid triggering of digits, nonsteroidal anti-inflammatory drug therapy, splinting, corticosteroid injection into the tendon sheath, and surgical release. Corticosteroid injections into the tendon sheath has been especially found to be beneficial in patients with disease duration of less than 6 months and having nodular type of disease. In these patients, the success rate of a single injection is as high as 96%.

Calcific Shoulder Periarthritis (Tendinitis)

Calcific tendinitis is a painful condition most commonly affecting the shoulder in which calcium hydroxyapatite crystals deposit predominantly in periarticular areas. In the

shoulder, these crystals may also deposit within the tendons of the rotator cuff. The incidence of calcific shoulder periarthritis is increased amongst patients with DM. Calcific tendinitis may coexist with adhesive capsulitis in the shoulder.

Carpal Tunnel Syndrome (CTS)

Carpal Tunnel Syndrome is a common compression neuropathy of the median nerve associated with many conditions including diabetes. Classically, these patients present with the wasting of the muscles of the thenar eminence (abductor pollicis brevis, extensor pollicis longus, and extensor policis brevis). The typical presentation is hand paresthesia involving the median nerve distribution. Paresthesia and pains are usually exacerbated in the night. Apart from diabetes, CTS is also associated with rheumatoid arthritis, pregnancy, and obesity. Diabetes may induce structural alterations of tendon, increase obesity, and produce metabolic abnormalities that result in proliferation or fibrosis of the connective tissues surrounding the nerve. Transforming growth factor-beta has a key role in the pathogenesis of CTS. Increased TGFb is seen in TGF which is associated with increased localized inflammation and collagen deposition. The prevalence of CTS in diabetes has been reported at 11–25%, and it is more common in women. Conversely, 5–8% of patients with carpal tunnel syndrome may have diabetes. Two classic signs, Tinel's sign and Palen's test, are very helpful in establishing the diagnosis. A positive Tinel's sign refers to the elicitation of paresthesia and/or pain in the hand (mainly thenar and thumb area) by tapping over the median nerve on the volar aspect of the wrist. Palen's test is positive if similar symptoms are produced when the patient flexes both wrists completely and opposes the dorsal surfaces of the hands to each other.

Management focuses on analgesics and splints, while topical steroid injection and surgery may be indicated in more severe cases. Endoscopic tendon release procedures are increasingly being used in CTS to relieve the median nerve from compression, with good clinical outcomes. Recent studies have suggested that a single dose of ultrasound-guided perineural platelet-rich plasma (PRP) injection can provide therapeutic effect for at least 1 year post injection [7].

Reflex Sympathetic Dystrophy

Also known as algodystrophy, Sudeck's atrophy, and chronic regional pain syndrome type 1, this disorder is characterized by pain, swelling, trophic changes, and vasomotor disturbances with impaired mobility of the body part involved. The development of the condition is usually preceded by a trauma, which may range from trivial injury to a surgery or a fracture. Apart from diabetes, reflex sympathetic dystrophy is also seen in hyperthyroidism, hyperparathyroidism, and type IV hyperlipidemia. A large variety of treatment options have been used in reflex sympathetic dystrophy ranging from analgesics, physiotherapy, intravenous bisphosphonates, calcitonin, oral corticosteroids, and sympathetic ganglion blocks. Clinical outcomes are usually good. In rare patients, it may lead to contractures.

Diffuse Idiopathic Skeletal Hyperostosis (DISH), Forestier's Disease

Diffuse idiopathic skeletal hyperostosis (DISH) is a condition characterized by ossification of spinal ligaments associated with large bridging osteophytes between vertebral bodies. Obesity, hyperlipidemia, hyperuricemia, hypertension, hyperinsulinemia, and diabetes are thought to be associated with DISH.

The diagnosis of DISH is based on radiologic features. Radiographic criteria for the diagnosis of DISH include the presence of 'flowing' osteophytes along the anterolateral aspects of at least four contiguous vertebral bodies, the preservation of intervertebral disk spaces, and the absence of changes of degenerative spondylosis or spondyloarthropathy. Analgesics, heat application, exercise, and local corticosteroid injections have been used to treat patients with DISH. Targeted spine strengthening exercise and posture training program reduced kyphometer measured, but not radiographic-measured kyphosis in people with DISH [8].

Crystal-Induced Arthritis and Gout

Calcific tendinitis is clearly associated with diabetes. Similar calcific processes certainly occur in blood vessels of diabetic patients as well as in spinal ligaments in DISH. Metabolic changes, consequent to chronic high glucose and insulin levels, may produce important changes in connective tissues that might predispose to pathologic calcification.

Gout is an inflammatory arthropathy characterized by increased deposition of mono-sodium urate crystals in the joint. Gout is more common in Caucasians where it effects 1–2% of the population. Risk factors for gout include hyperuricemia, male sex, renal impairment, alcohol use, and increased consumption of meat. Insulin resistance, which is very common is type-2 diabetes, is associated with decreased uric acid excretion and hence is associated with hyperuricemia. Serum urate concentration and gout is strongly associated with central adiposity and insulin resistance. Few meta-analysis have showed that the prevalence of gout in type-2 diabetes may be as high as 25%. It must be highlighted

that amongst the anti-hypertension medicines and anti-lipid medication, losartan and fenofibrate have urate-lowering effects. Hence, special consideration should be given to these drugs when type-2 diabetes patients with hyperuricemia/gout is planned to be put on hypertension or lipid medications. Mycophenolate mofetil therapy with pegloticase and anakinra are new upcoming therapies for refractory gout [9, 10].

Osteoarthritis

Osteoarthritis is the most common form of arthritis in adults and as such would frequently co-occur with diabetes by chance alone. Clear clinical evidence that diabetes predisposes to premature or severe osteoarthritis is lacking. The fact that obesity is a common risk factor for both osteoarthritis and diabetes makes epidemiologic studies difficult. Peripheral neuropathy may also adversely affect joints and increase the risk of advanced, aggressive forms of osteoarthritis. There seems to be propensity for diabetic patients to have more severe pain and radiographic changes both preoperatively and postoperatively, an increased risk of deep tissue infection as well as an increased revision rate compared with nondiabetic controls. Whether insulin resistance worsens or not when therapeutic doses of oral glucosamine are used to treat osteoarthritis remains controversial. Intra-articular injections of autologous fat with or without platelet rich plasma is a new upcoming therapy for severe osteoarthritis [11].

Charcot Arthritis

Charcot's arthropathy is a form of destrictive arthritis. It is seen in diabetes usually as an association with peripheral neuropathy. It is a debilitating condition observed in 0.4% of patients with diabetes and is associated with limb deformity, gait instability, ulcers and may lead to limb amputation also. Four different stages of Charcot arthropathy have been described. In the earliest stage (Stage 0), the patient usually complains of pain in the joint. The join may or may not have swelling. X-rays of the joint are normal at this stage. MRI is the most sensitive tool for diagnosis at this stage where it can pick up marrow edema, subchondral cysts, and microfractures. In Stage 1, the X-rays of the joint now start showing varying degrees of osteolysis, bone fragmentation, and architectural destruction. Stages 0 and 1 are the clinically active stages of the disease characterized by joint pain swelling, redness, and localized increase in skin temperature. In stage 2, the clinical signs of local inflammation usually resolves, coalescence starts which may be visible on joint X-rays. Stage 3 is known as the reconstructive stage, where fusion or ankylosis of the bones occur. Stages 0 and 1 usually last up to 6 months whereas stages 2 and 3 last up to 24 months.

Charcot's arthropathy most commonly involves the foot. Altered architecture of the foot as a result of the deformity leads to abnormal foot pressure distributions, leading to increased risk of foot ulcers at the high pressure points. Tarsometatarsal followed by the mid-tarsal joint involvements are the two most common types of Charcot arthropathy. After foot, knees, elbows, and the shoulder joints are most commonly affected by Charcot's arthropathy.

The pathogenesis of Charcot's arthropathy is yet to be fully elucidated. Localized joint inflammation and osteoclast activation is central to the pathogenesis of Charcot arthropathy. Increased local levels of tumor necrosis factor alpha, interleukins (IL-1, IL6), RANK ligand have been documented in Charcot arthropathies. Abnormal weight bearing due to diabetic neuropathy leads to small microtrauma to the foot, which leads to foot inflammation and hyperemia which sets up a vicious cycle of joint inflammation and damage resulting to Charcot arthropathy.

The most important aspect of managing Charcot arthropathy, especially in the acute stage is joint immobilization, and absolute cessation of weight bearing. Nonweight bearing total contact cast (TCC) is the treatment of choice for managing Charcot foot. This leads to significant reduction in joint inflammation and reduces the risk of deformity also. Bisphosphonates (pamidronate, alendronate, zoledronate) have been demonstrated to be useful in reducing joint inflammation and hastening recovery in patients with Charcot arthropathy, both in observational studies as well as randomized controlled trials. Small studies have also showed the beneficial effects of RANK ligand inhibitors (denosumab) in the management of Charcot arthropathy. Surgery has no role in the management of Charcot arthropathy in the active stage. Surgery has a role in inactive or burnt out stage of the disease, where it helps in joint stabilization, and helps improving the pressure distribution of the joint, which would help in preventing ulcers. Therapeutic footwears have an important role in improving foot pressure distribution in patients with Charcot's foot, help in healing of foot ulcers, and also providing limited mobility to the patients.

Diabetic Foot

One of the most devastating complications of diabetes is diabetic foot. Foot problems in diabetes occur due to combination of abnormalities affecting vascularity, peripheral nerves, skin and musculoskeletal system.

Foot problems in diabetes can be largely divided into infective and noninfective complications.

Charcot's foot is characterized by destruction of small foot joints and complete disorganization of anatomy of foot. Neuropathy is the main contributor in this condition with both peripheral and autonomic neuropathy playing

significant roles. Peripheral neuropathy makes the insensate foot take repeated trauma and also to transmit pressure in not-so-optimal way. This creates false pressure points and puts undue stress on small joints of foot. Autonomic neuropathy, on the other hand, impairs regulation of blood flow to foot and thus exposing bones of foot to excessive bone loss during periods of increased blood flow. Charcot foot is great danger to health of any diabetic as this condition cannot be reversed and puts patient at grave risk of foot ulcer and infections. It can present early on, as an acute inflammatory process which is frequently mistaken for gout, osteomyelitis or injury, and then develops into chronic arthritis with severe deformities. It is always a clinical challenge to differentiate between Charcot foot and osteomyelitis. Systemic signs of infection (fever, leucocytosis), breach in skin of foot, positive probe test and positive labeled leucocyte scan favor a diagnosis of osteomyelitis. MRI and Tc bone scan have also been used to differentiate between them.

Proper foot care education to patient to avoid further deterioration and to prevent ulcers is of paramount importance. Non-weight bearing and immobilization of the affected limb have been the mainstays of therapy. Bisphosphonates have also been reported to be useful for the acute phase of Charcot arthropathy.

A detailed discussion of ulceration and infective complications of foot in diabetes is beyond the scope of this chapter. However, general principles for wound care remain the same. There are two ways in which diabetic foot is at disadvantage. One, diabetic foot is more predisposed to trauma. Any skeletal abnormality in foot in patient with diabetes predisposes them to increased risk of trauma because of sensory loss. Diabetic patients with minor trauma to foot are more likely to ignore because of lack of pain. Insensate foot also alters proprioception and thus makes these patients more prone to falls and major trauma while walking. Moreover, neuropathy further contributes to deformity of foot, e.g. atrophy of mid-foot muscles causes clawing. Associated autonomic neuropathy results in dry skin and more risk of fissures. Second, altered blood supply to foot, due to vasculopathy, makes these trauma and infection difficult to heal. Moreover, delivery of antibiotics is also hampered. And because of this reason, patient vasculature is a must for a normal foot in diabetics. In the presence of vascular adequacy, even if minor wounds are sustained they would heal with basic care.

The main goal should be prevention of diabetic foot ulcers. In this regard, at-home foot skin temperature monitoring is a great way to predict sites of increased risk of foot ulcer. At-home foot temperature monitoring significantly reduces incidence of diabetic foot ulcer recurrence at or adjacent to measurement sites over usual care, only if the participants reduce ambulatory activity when hotspots are found or when aiming to prevent ulcers at any foot site [12].

Conclusion

Musculoskeletal complications of diabetes hence are a large number of diverse set of disorders. In contrast to other complications of diabetes, a good clinical eye has a key role in the diagnosis of these disorders. Many a times, these complications are missed in a busy clinic practice, as most of these complications are not severe and life threatening, although lack of their diagnosis and timely treatment may lead to significant morbidity in the patients.

Multiple Choice Questions

1. Anti-diabetic medications linked with adverse impact on bone health include:
   (a) Sulfonylureas
   (b) Insulin
   (c) **SGLT-2 inhibitors**
   (d) DPP-4 inhibitors
   (e) **Glitazones**
2. All of the following are true regarding diabetic myonecrosis except:
   (a) Painful
   (b) ESR is raised
   (c) Spontaneously resolving.
   (d) **Recurrence rates are low**
   (e) Asymmetrical
3. All of the following are true regarding diabetic amyotrophy except:
   (a) Asymmetrical
   (b) Predominantly motor involvement and muscle wasting.
   (c) Spontaneously resolving.
   (d) **Definitive role of immunosuppresive and glucocorticoids in management**
   (e) **Sensory involvement is absent**
4. Most commonly involved joints in adhesive capsulitis in patients with diabetes:
   (a) Knee
   (b) **Shoulder**
   (c) Hips
   (d) Elbow
   (e) Metacarpophalangeal
5. Carpel tunnel syndrome leads to wasting of the following small muscles of the hand except:
   (a) abductor pollicis brevis
   (b) **abductor policis longus**
   (c) extensor pollicis brevis
   (d) extensor policis longus
   (e) **Opponens pollicis**
6. Carpel tunnel syndrome is due to the involvement of the following nerve:
   (a) Ulnar nerve
   (b) **Median nerve**

(c) Radial nerve
(d) Cutaneous nerve of the forearm
(e) Superficial peroneal nerve

7. Antihypertensive medications with uric acid lowering effects include.
   (a) amlodipine
   (b) ramipril
   (c) lisinopril
   (d) olmesartan
   (e) **losartan**
8. Anti-lipid medication with uric acid lowering properties
   (a) **Fibrates**
   (b) statins
   (c) bile acid binding resins
   (d) PCSK9 inhibitors
   (e) Ezetimibe
9. Medications acting on bone metabolism found to be beneficial in Charcot's arthropathy include:
   (a) teriparatide
   (b) **bisphosphonates**
   (c) calcitonin
   (d) **denosumab**
   (e) saracatanib
10. The pathogenesis of Charcot's arthropathy involves all except:
   (a) increased inflammatory cytokines
   (b) increased osteoclast activation
   (c) **decreased RANK-L expression**
   (d) **increased osteoblast activation**
   (e) increased local hyperemia.

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Diabetes and the Skin

61

Justine Mestdagh, Sterre Blanche Laura Koster, Jeffrey Damman, and Hok Bing Thio

Chapter Objectives/Key Features

- There are several skin manifestations in diabetes mellitus, some of them occur frequently.
- Some of these are specific for Type 1 diabetes mellitus, others for Type 2 and some occur in both.
- Medications used to treat diabetes mellitus may also cause skin adverse effects.

Introduction

Many diabetes mellitus patients develop skin manifestations during the course of the disease and children are no exception [1, 2]. Prevalence rates range from 30 to 80% [2, 3]. However, we should keep in mind that diabetes is a highly prevalent disease and therefore should remain critical toward studies trying to determine a direct relationship without being aware of possible confounding factors. The skin is a large organ of the human body and is directly visible to the outside world. Because of this, patients tend to care a lot about their skin, sometimes more than clinicians realize [4].

Skin manifestations of diabetes mellitus are diverse and range from cosmetic concerns to severe conditions more frequently seen in long-standing disease. Recognizing these is a rewarding clinical skill to master, since some of them may be important diagnostic clues as well as markers of advanced disease [5]. Some diabetes-related skin defects can be a port of entry for later infections. Several medications can affect the skin shortly after intake. Some skin manifestations are more specific for diabetes than others. Besides evaluating the skin for establishing a diagnosis of diabetes, it can also be a help for evaluating treatment success, study results, and glucose levels.

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Pathogenesis

Pathogenesis of skin involvement in diabetes mellitus can be seen as a collaborative, cumulative phenomenon of biochemical, vascular, neurological, immune-mediated and metabolic changes with longstanding hyperglycemia as its key pathogenic player. Diabetics with hemoglobin A1c values <8 mmol/ml tend to have less cutaneous involvement than those with hemoglobin A1c values >8 mmol/ml [2].

Increased oxidative stress and chronic high levels of circulating glucose lead to a non enzymatical chemical reaction between glucose and proteins, lipids and nucleic acids. The chemical reactions between amino acids and the carbonyl group of glucose are called Maillard reaction. First reversible Schiff's bases are formed followed by the conversion to stable products. Finishing transforming chemical reaction leads to the formation of advanced glycation end products (AGE) which bind to specific receptor on many cell surfaces initiating numerous intracellular signaling cascades leading to diabetic complications [6]. Due to formation of AGE and oxidative stress, vascular damages appear [7]. Neuropathy leads to hypo- or even anhidrosis, vascular dilation causing erythema and hyposensation. Vascular and neurological changes are responsible for loss of sensation, impaired blood supply, and failure of homeostatic regulatory mechanism in end organs such as the skin.

Today, skin autofluorescence (SAF) can be measured easily by a quick, non-invasive method. The SAF serves then as

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a quantitative parameter of the cutaneous AGE which in turn can be used to predict and early detection of diabetic vascular complications [8].

Hyperglycemia increases the flux through to pyolol- and hexosamine pathways with activation of protein kinase C, NFkappa b, mitogen-activated protein kinase (MAPK), and others [9]. Consequently, this leads to endothelial proliferation and basement membrane thickening with deposition of periodic acid-Schiff stain positive (PAS+) material with narrowing of arterioles, capillaries, and venules.

Keratinocyte function is frequently altered which leads to an impaired epidermal barrier function and delayed wound healing. [10–12] Decreased hydration might play a role. pH values of the skin are higher than in non-diabetic patients leading to an increase in bacterial colonization.

Skin Manifestations of Diabetes Mellitus

Certain skin manifestations are specific for Type 1 diabetes mellitus, others for Type 2 and some occur in both. In the following text, diseases appear in alphabetical order. Whether they occur predominantly in Type 1 diabetes mellitus, 2, or both will be mentioned.

Acanthosis Nigricans

Acanthosis nigricans (Fig. 61.1) consists of velvety hyperpigmented plaques in the intertriginous areas of the skin. Frequently skin tags are found within these lesions. Most patients are asymptomatic although maceration, malodor, and discomfort have been reported. It is the most frequent skin condition in diabetes, almost all Type 2 diabetic patients develop acanthosis nigricans to a certain extent. It is more frequently seen in Hispanics and native as well as African Americans; men and women are equally affected. Besides diabetes, acanthosis nigricans can also appear in obese individuals, patients with insulin resistance (both independently associated) and less frequently in patients with acromegaly, Cushing syndrome, and leprechaunism. It is sometimes observed in malignancies (especially those of the stomach) and associated with certain medications, for example, nicotinic acid, corticosteroids, and rarely repetitive insulin injections. Lastly, it can appear in healthy individuals as well [13, 14].

Histopathology of the affected skin (Fig. 61.2) reveals hyperkeratosis, papillomatosis, mild acanthosis, and sometimes hyperpigmentation of the basal layer. There is usually no dermal inflammation. The hyperkeratosis causes the darkened aspect and papillomatosis causes accentuation of skin markings. High levels of circulating insulin bind the tyrosine

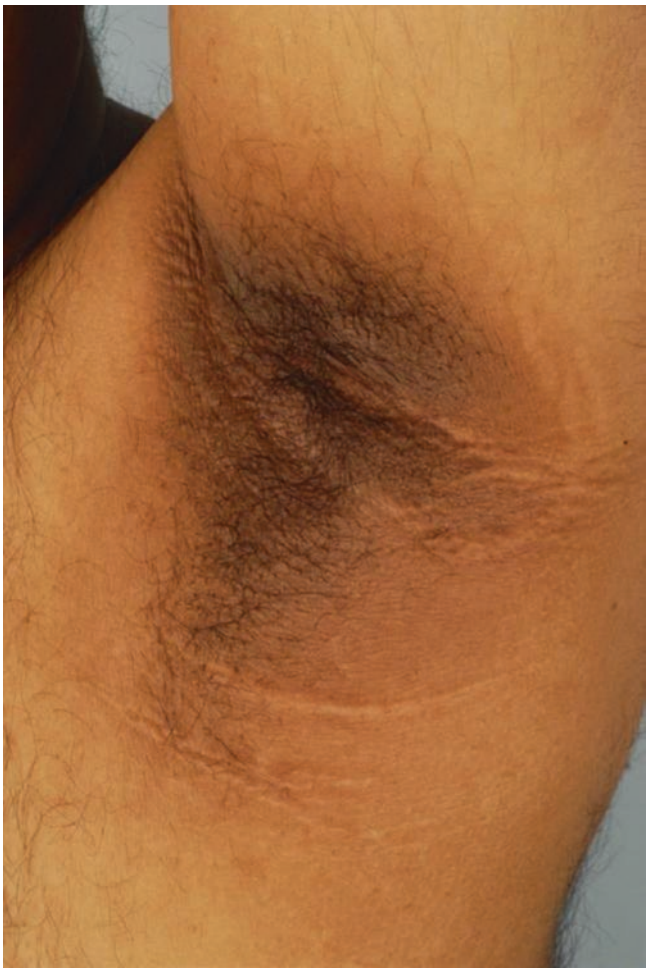

Fig. 61.1 Acanthosis nigricans

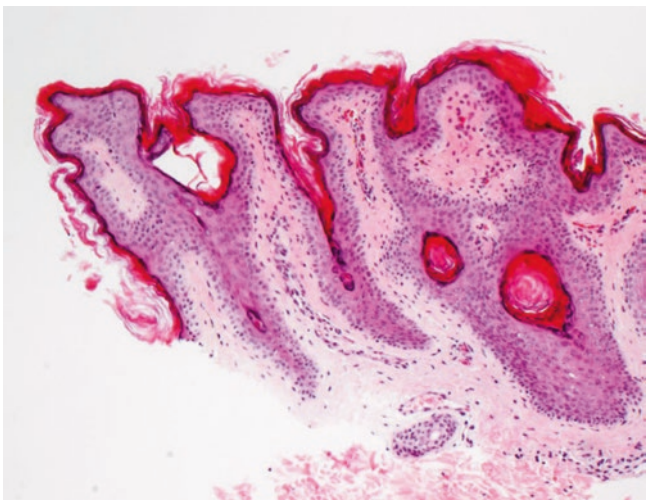

Fig. 61.2 Acanthosis nigricans. Acanthosis nigricans: the lesion shows hyperkeratosis and papillomatosis usually without dermal inflammation.

kinase growth factor receptors (e.g., insulin-like growth factor 1receptor) on fibroblasts and keratinocytes. This stimulates these cells to grow, causing the typical skin manifestations.

People with extensive acanthosis nigricans seem to have higher fasting plasma insulin levels [15, 16].

Weight reduction, exercise, and if necessary, glucose lowering treatment in combination with lipid lowering drugs may reduce insulin resistance and improve acanthosis nigricans. If patients experience discomfort, ointments containing salicylic acid, urea, lactic acid, or retinoids may reduce the hyperkeratotic lesions. Systemic retinoids have been used in severe cases. Recurrence is often seen after discontinuation of therapy.

Acrochordon

Acrochordon (Figs. 61.3 and 61.4), also called fibroma molle, fibroepithelial polyp, or skin tag is a soft pedunculated flesh colored papule in the axillae, neck, eyelids, and in the inframammary region. Patients are asymptomatic apart from possible cosmetic concerns and rarely experience pain or irritation when the fibroma contains nerve endings.

There is a slight female predisposition and its prevalence increases with age. The association between acrochordon and obesity is well established, but they are also an independent marker for diabetes, especially Type 2 [17]. Skin tags have been detected in 23% of diabetic patients compared to 8% in a healthy control group. Though there is some controversy regarding the total amount of skin tags per individual and the associated risk of diabetes, current literature seems to show that the higher the number, the higher the risk for diabetes mellitus. Patients with over 30 skin tags are especially at risk. A positive correlation has also been found between the total number of skin tags and mean fasting plasma glucose [18, 19] making skin tags an even more sensitive cutaneous marker for diabetes than acanthosis nigricans. Clinicians should be aware of this association when taking note of multiple acrochordons. As mentioned earlier, high levels of circulating insulin stimulate keratinocytes to grow, which could help explain the higher prevalence of skin tags in diabetics. Treatment is not necessary, but if patients want them to be removed, they can be excised. Electrodessication and cryotherapy are two valid alternatives.

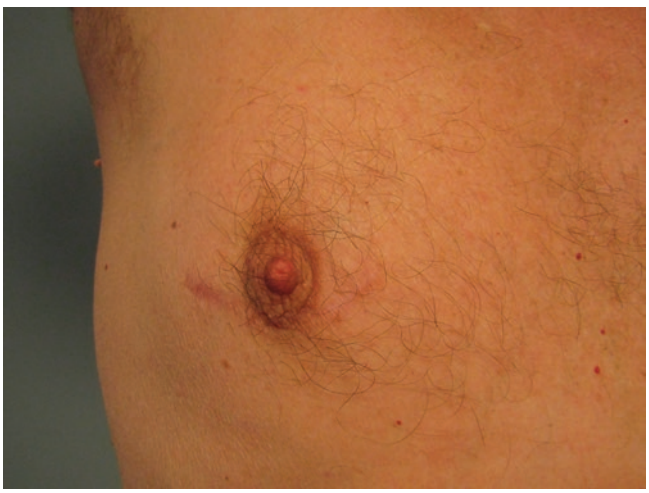

Fig. 61.3 Acrochordon in the right axilla

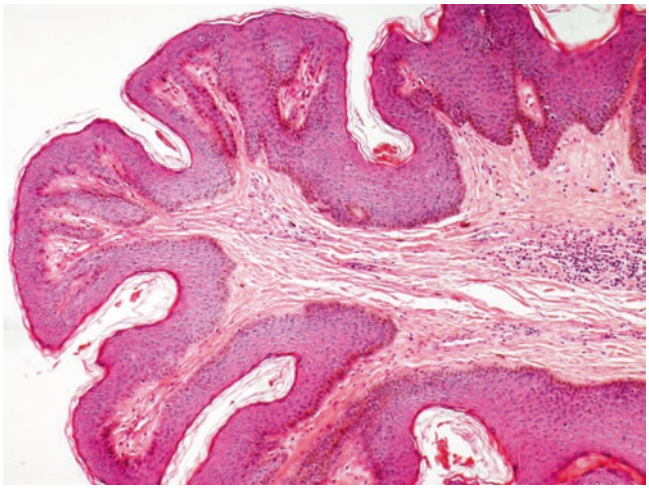

Fig. 61.4 Acrochordon. Acrochordon or fibroepithelial polyp: the papules show a fibrovascular core covered by epidermis showing hyperplasia sometimes resembling seborrheic keratosis. The stroma often shows loosely arranged collagen, an increased number of blood vessel and (in larger lesions) fat cells

Acquired Perforating Dermatosis

Acquired perforating dermatosis (Fig. 61.5) presents with scaly highly pruritic follicular hyperkeratotic dome-shaped papules and nodules, often with central umbilication or a central keratotic plug on the extensor surfaces of the lower extremities and in some cases also on the face, trunk, and dorsal area of the hands.

This chronic disease is rare but more frequently seen in Afro-Americans with diabetes (both Type 1 and 2) and chronic kidney disease or hemodialysis (as high as 10%). However, it can also occur in diabetics with normal kidney function [20–22].

Skin conditions to be included in the differential diagnosis are prurigo nodularis, folliculitis, arthropod bites, multiple keratoacanthomas, psoriasis vulgaris, and lichen planus. Pathologic examination (Figs. 61.6 and 61.7) shows a hyperplastic invaginating epidermis containing parakeratosis, degenerated connective tissue and cellular debris, following the transepidermal elimination of dermal collagen and elastin.

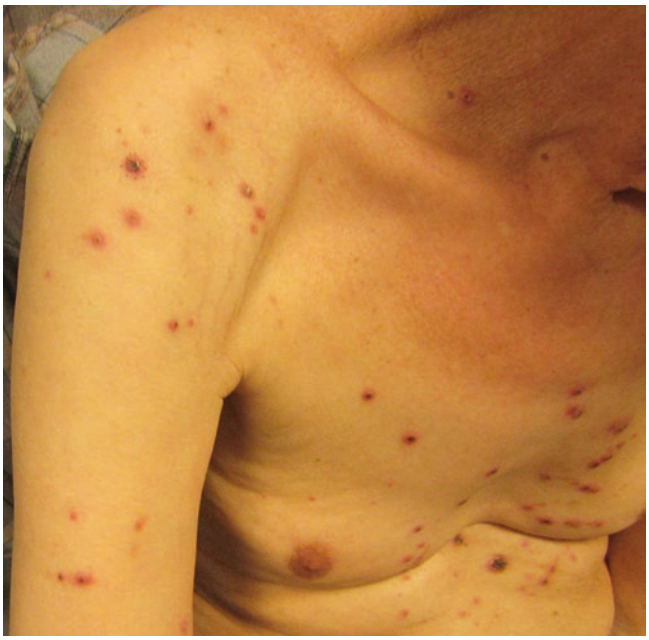

Fig. 61.5 Acquired perforating dermatosis

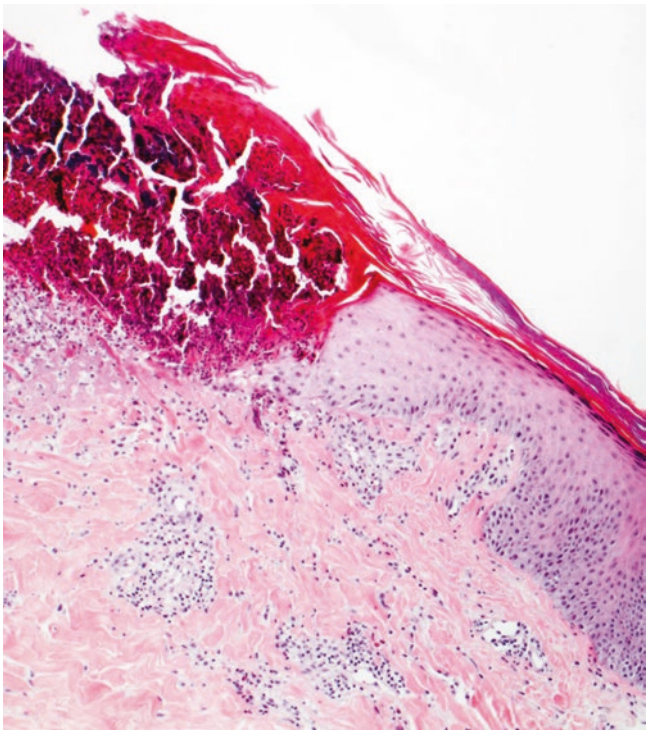

Fig. 61.6 Acquired perforating dermatosis. The lesion shows an invaginating epidermis containing a parakeratotic plug with degenerated connective tissue fibers and cellular debris

The cause is probably a multifactorial interplay between glycation of collagen, Koebner phenomenon, microvasculopathy, and inflammatory reaction to altered dermal collagen or deposition of substances which are not removed by dialysis. It is unclear whether the abnormality appears

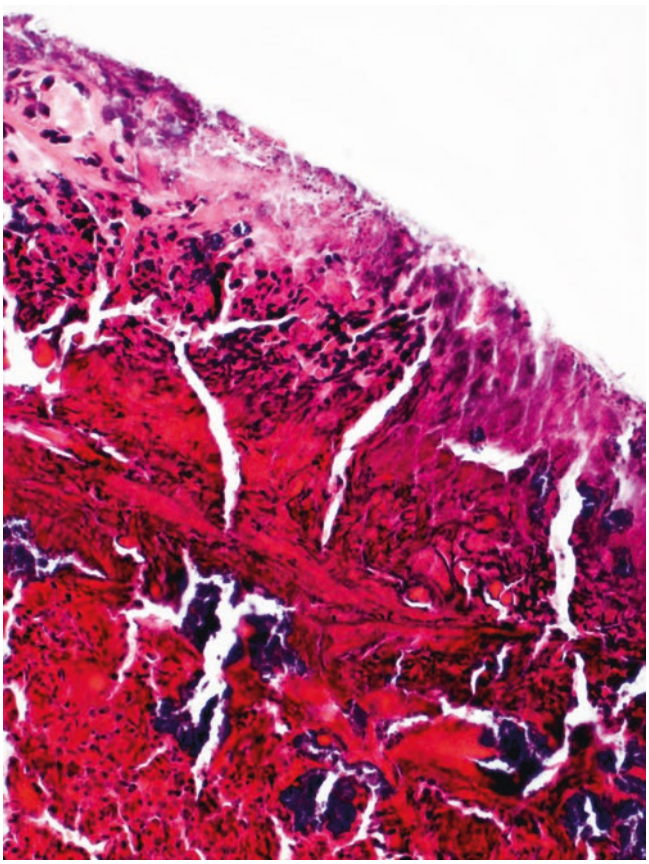

Fig. 61.7 Acquired perforating dermatosis. The lesion shows an invaginating epidermis containing a parakeratotic plug with degenerated connective tissue fibers and cellular debris

first in the dermis or epidermis, pruritus is probably rather the cause of these changes than the effect. Acquired perforating dermatosis is difficult to treat. Treating the pruritus is the main goal. Coexisting disease should be treated according to current standards though dialysis does not improve the disease course. Topical glucocorticoids, antihistamines, topical and systemic retinoids, doxycycline, allopurinol, cryotherapy, and phototherapy are all used for symptom relief.

Bullosis Diabeticorum

Patients suffering from bullosis diabeticorum present with uni- to bilateral spontaneous tense non-inflammatory bullae on normal appearing skin of the dorsolateral sides of the lower extremities and sometimes of the hands. Though it is thought to be a distinct marker for diabetes, it is the rarest skin manifestation in diabetes occurring in 0.5% of all diabetic patients. No large population studies have confirmed this so its frequency might be higher. It does occur more in men with longstanding poorly controlled Type 1 diabetes mellitus with peripheral neuropathy [23, 24].

There are three known subtypes. In the first, "classic" type, the cleavage level of the bullae is intraepidermal [25], the fluid in these bullae is clear and sterile and the surrounding epidermis shows spongiosis. There is no pain. These bullae resolve spontaneously without scars in a few weeks but recurrence is possible. Histopathological examination shows a subepidermal blister with early re-epithelialization. The second type consists of bullae filled with hemorrhagic fluid. The cleavage level lies below the dermoepidermal junction. Healing comes with scarring and atrophy. The third type appears on tanned skin, and its cleavage level lies within the lamina lucida of the dermoepidermal junction. Healing leaves no scars. The differential diagnosis of bullosis diabeticorum includes primary autoimmune blistering such as pemphigus, bullous pemphigoid, erythema multiforme, epidermolysis bullosa acquisita, and porphyria cutanea tarda. Immunofluorescence tests are negative. Bullosis diabeticorum is associated with high blood glucose levels but venous pressure elevation may also play a role. Microangiopathic vessels offer less blood to the skin which then becomes more prone to acantholysis, and thus blister formation. Other possible causes are autoimmune phenomena, exposure to UV light, and alterations in calcium and magnesium levels [23, 26, 27]. Spontaneous resolution is seen within 2 to 5 weeks [28]. No treatment is needed besides the prevention of complications, e.g., chronic ulcers and bacterial infections. In cases of major discomfort, aspiration can be considered. Nevertheless, recurrence of bullae is frequent.

Diabetic Cheiroarthropathy (Diabetic Stiff Hand or Limited Joint Mobility Syndrome)

People with diabetic cheiroarthropathy have a thickened waxy skin and bilateral limited joint mobility of the hands and fingers leading to flexion contractures (e.g., Dupuytren's disease). This process starts at the fifth digit and progresses radially. It can extend to the wrists, elbows, ankles, knees, toes, and cervicothoracic spine. Clinical examination can reveal a prayer sign, which is the inability to approximate the palmar surfaces of the hands and fingers. Some patients have Huntley papules, which are multiple tiny papules grouped on the dorsal sides of the fingers or periungally. On histologic examination, a hyperkeratotic epidermis and dermal papillary hypertrophy is noticed. Up to 30% of diabetics have diabetic cheiroarthropahty. Incidence increases with disease duration but not with diabetes control. Although it is more common in patients with Type 1 and Type 2 diabetes mellitus than in other individuals, the disease can occur in people without diabetes. If presenting in diabetic patients, it is a predictor of other complications (especially retinopathy and nephropathy). In children with Type 1 diabetes, it is the earliest clinically apparent long-term complication [1].

Differences in the collagen household of the skin such as increased glycosylation of collagen lead to irreversible crosslinking of collagen and other proteins and decreased collagen degradation. Other possible contributing factors are microangiopathy, neuropathy [29, 30], and accumulation of AGE which, after binding their receptors, would stimulate inflammatory and fibrogenic growth factor receptors and cytokines via protein kinase C.

Diabetic cheiroarthropathy is not yet treatable but control of diabetes and physiotherapy are likely to be helpful. Phototherapy, radiotherapy, prostacyclin, penicillin, ciclosporin, factor XIII, and sorbinol have been applied without spectacular results. Research in animals is currently underway, investigating drugs blocking the protein crosslinking or blocking interactions between AGE and their receptors in the early stages of the disease.

Diabetic Dermopathy

Lesions of diabetic dermopathy or so-called shin spots are dynamic, various stages can present in the same patient at the same time. They are usually asymmetrical, 0.5 to 1 cm large red to brown hyperpigmentated spots ranging from atrophic macules to plaques. Plaques are more frequently recognized. These appear bilateral on the extensor parts of the legs but can rarely occur elsewhere and are usually asymptomatic. It is one of the most common skin manifestations in diabetes (Type 1 and 2) with a prevalence of up to 70%, although it is rare in children [1]. It is more frequent in men aged 50 and over and patients with poorly controlled diabetes. Although the association is strong, it is not entirely specific for diabetes mellitus since 20% on nondiabetic people have similar lesions [3]. Patients presenting with this dermopathy should be screened for diabetes especially if they present with four or more shin spots because they are thought to represent postinflammatory hyperpigmentation and cutaneous atrophy in the setting of poor vascular supply and microtrauma [31].

Shin spots may precede abnormal glucose metabolism but may also be a marker for microangiopathic complications such as retinopathy, nephropathy, and neuropathy, as well as macroangiopathic complications, especially coronary artery disease [32, 33]. Differential diagnosis with dermatophytosis should be made. Diabetic dermopathy should be a clinical diagnosis, and there is no need for skin biopsy. If performed, a specific histopathologic findings are seen such as hyperpigmentation of the epidermal basal layer, hemosiderin and melanin in the dermis, and thickening of the arteriolar basement membrane. There is no effective treatment but some lesions resolve spontaneously in 18–24 months on average though atrophic hypopigmented scars are seen afterward. Infection prevention can be indicated and new lesions may always arise.

Disseminated Granuloma Annulare

Granuloma annulare (Fig. 61.8) is a rare benign inflammatory disease. The main efflorescences are erythematous papules which slowly expand centrifugally and resolve centrally to reveal annular plaques with superficial scaling. The back of the hands and arms are usually affected. Patients are usually asymptomatic but can experience pruritus. The disease can occur at any age but is mostly seen in children and adolescents. Multiple subtypes exist. Its relation to diabetes has been the subject of many discussions over the years and now only the disseminated form is believed to be associated with diabetes and even this correlation is only based on retrospective studies and currently no case control studies are available [34, 35]. Generalized granuloma annulare can also be seen in malignancies, thyroid dysfunction, hepatitis B, C and HIV infections [36–40]. Histology reveals a granulomatous reaction pattern showing palisading of histiocytes (and sometimes giant cells) and lymphocytes surrounding an area of necrobiotic/collagenolytic collagen (complete type) (Fig. 61.9). The necrobiotic areas show deposition of mucin. The incomplete type shows interstitial inflammation with histiocytes (sometimes admixed with giant cells) and lymphocytes and also mucin deposition can be found (incomplete/interstitial form). Pathologists sometimes have difficulties differentiating this disease from necrobiosis lipoidica because both present with infiltrating palisaded histiocytes and collagen degeneration in the dermis. In the disseminated form, inflammation may be mild and the areas of inflammation are often found in the papillary dermis as seen in lichen nitidus. Also, necrobiosis and mucin deposition might be less profound. Not only pathologists have a hard time differentiating these diseases, they are also clinically resembling and might even coexist. Some authors suggest that generalized granuloma annulare is an early phase of necrobiosis lipoidica, [41] although in the former no epidermal atrophy or yellow discoloration is seen.

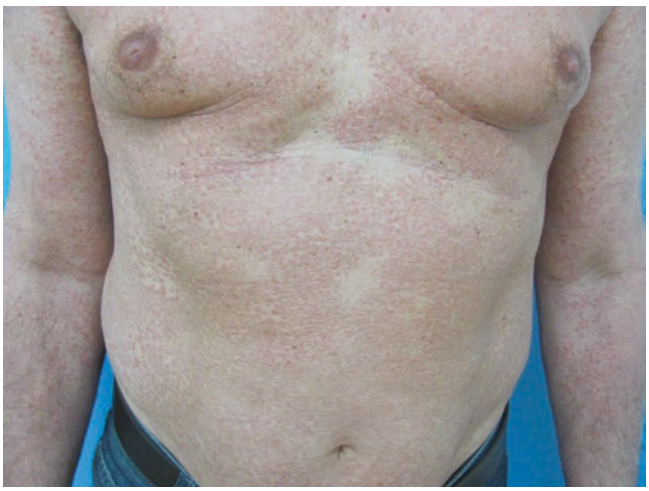

Fig. 61.8 Disseminated granuloma annulare

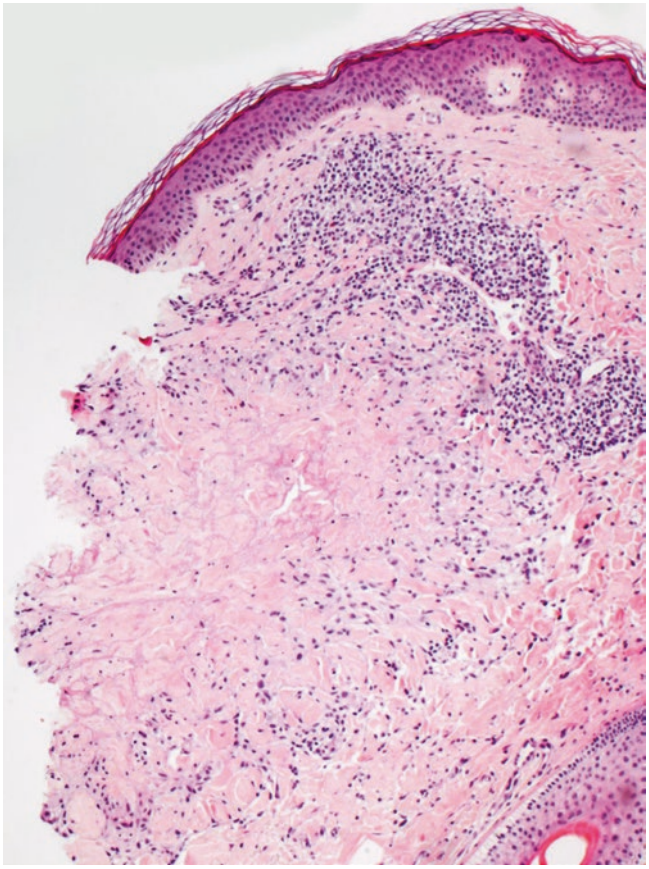

Fig. 61.9 Disseminated granuloma annulare. Areas of necrobiosis are surrounded by palisading histiocytes and lymphocytic inflammation. Although the histopathological features can be identical to classical granuloma annulare, disseminated granuloma annulare often shows a mild infiltrate located in the papillary dermis.

In contrast to localized forms, generalized granuloma annulare only rarely resolves spontaneously. A protracted and relapsing course is usually seen with often therapy-resistant lesions. Many different types of treatment have been used including cryotherapy, topical, intralesional or systemic corticosteroids, phototherapy (UVA1 and PUVA), chlorambucil, pentoxifylline, cyclosporine, fumaric acid ester derivatives, potassium iodide, niacinamide, etanercept, infliximab, adalimumab, efalizumab, hydroxychloroquine, and dapsone.

Eruptive Xanthomas

Eruptive xanthomas are small (1–2 mm) yellow papules with erythematous border appearing in weeks to months, mostly asymptomatic but sometimes tender. They appear most frequently on the extensor surfaces of the limbs and the buttocks. Lesions often occur as a result of Koebner phenomenon on pressure sites. The yellow discoloration is due to foamy

macrophages in the dermal inflammatory infiltrate of lymphocytes and neutrophils. They are associated with elevated eruptive triglycerides in the blood of patients with poorly controlled diabetes (especially Type 2), in familial hypertriglyceridemia and in patients using excessive amounts of alcohol. Insulin stimulates the activity of lipoprotein lipase and plays a role in the metabolism of triglycerides. This leads to a decreased clearance of very low density lipoproteins and chylomicrons. This can be aggravated further by polyphagia caused by glycosuria [42, 43]. Clinicians should be aware of a significantly elevated risk of pancreatitis [44]. Only 0.1% of patients with diabetes will develop eruptive xanthomas. The main treatment objective is controlling the hypertriglyceridemia and to be aware of other problems related to this condition. Control of diabetes and hyperlipidemia leads to swift disappearance of the xanthomas. Local therapeutic options are application of trichloroacetic acid, excision, curettage, and CO_2 laser therapy.

Infections

Recurrent skin infections may be the presenting feature of diabetes. Bacterial and fungal infections appear more frequently, more severe, and atypical. Skin infections occur in 20–50% of diabetic patients, more frequently in Type 2 and are associated with poor glycemic control. Patients with well-controlled diabetes are not at higher risk of infections. Viral infection on the contrary are not more frequent. For further details, we refer to Chap. 66 on infections.

Lichen Planus

Lichen planus (Fig. 61.10) is a chronic inflammatory disease of the skin, mucous membranes, scalp, and nails. Lesions are pruritic and present as flat-topped polygonal violaceous papules. Wickham striae can be visible on oral mucosa only and consist of a fine reticular network of white arborizing lines but lichen planus can also affect genital mucosa. Four Ps (pruritic, purple, polygonal, and papules or plaques) can be used as a mnemonic. The exact pathogenesis of lichen planus is not clear but it has been postulated to be a T-cell-mediated autoimmune process, resulting in damage of keratinocytes [45–47]. Microscopic examination of a skin specimen reveals specific changes consisting of a lichenoid lymphocytic infiltrate with liquefactive degeneration (Fig. 61.11). Half of the patients with lichen planus have impaired glucose metabolism and approximately 25% suffer from diabetes. The reverse relationship has been examined much less, and the association is still controversial. Prevalence ranges from 0.9 to 1.4% in the general population vs. 2 to 4% in patients with either Type 1 or 2 diabetes [48–50]. Although the disease is usually self-limiting, patients are frequently treated. Topical corticosteroids should be tried first. If necessary other options include oral corticosteroids, oral retinoids, cyclosporine, and phototherapy which have all shown efficacy.

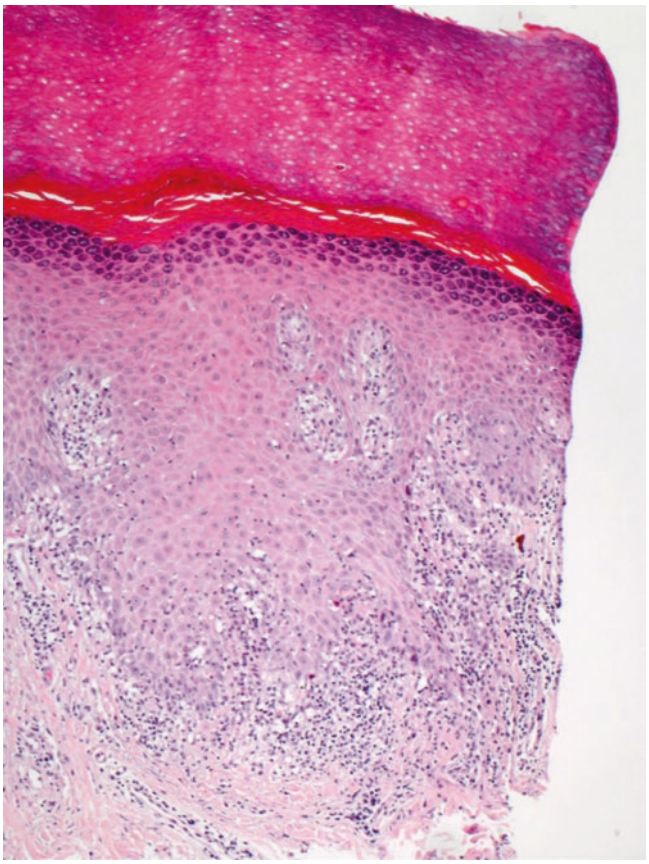

Fig. 61.10 Lichen planus. The lesion shows hyperkeratosis, acanthosis, and a lichenoid interface dermatitis with scattered apoptotic cells along the basement membrane

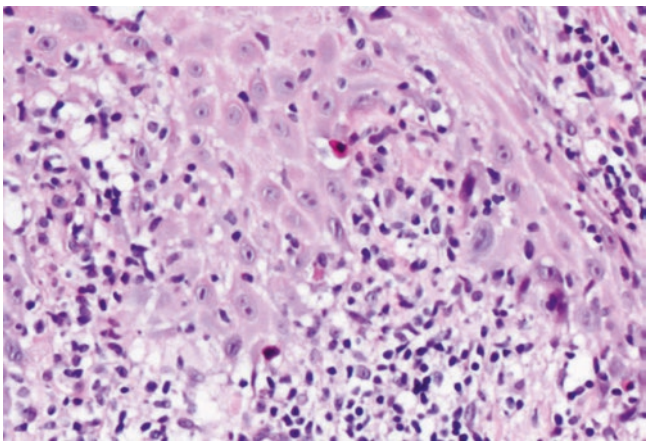

Fig. 61.11 Lichen planus. An interface dermatitis is noted with scattered apoptotic keratinocytes along the basal layer

Necrobiosis Lipoidica

Necrobiosis lipoidica (Fig. 61.12) is a chronic inflammatory skin disorder of collagen degeneration with a granulomatous response, thickening of the blood vessel walls and fat deposition [51]. A small clinical study determined that patients with necrobiosis lipoidica had a higher proportion of natural antibodies against such as actin, myosin, keratin, desmin when compared to patients with Type 1 diabetes mellitus and healthy control subjects [52, 53]. The disease is typically seen in patients in the third to fourth decade. Normally patients are asymptomatic though pain and pruritus can occur. Necrobiosis lipoidica starts with bilateral non-scaling red papules mostly seen on the pretibial regions though other regions can be involved. Red-brown rims may indicate disease activity. There is a centrifugal spreading pattern. Red papules slowly turn into atrophic lesions with central yellow discoloration possibly due to underlying dermal fibrosis and lipid excess in the dermis or due to the formation of advanced glycation end products, especially 2-(2-furoyl)-4[5]-(2-furanyl)-1H-imidazole which has a yellow hue. Telangiectasia can be seen through the translucent plaque. In advanced disease, large plaques can be seen and 35% of the lesions show ulceration. It should be known that chronic ulceration is a risk factor for the development of squamous cell carcinomas. Necrobiosis lipoidica is generally recognized in association with diabetes mellitus, however, the precise biological association remains unclear. In addition, quite recently necreobiosis lipoidica also has been associated with obesity, hypertension, dyslipidemia, and thyroidal disorder [54, 55]. The prevalence of necrobiosis lipoidica ranges from 0.3 to 1.2% in all diabetics to 2 to 3% in the insulin-dependent subtype. Even higher percentages in female patients have been reported. Necrobiosis lipoidica is thought to be the best recognized skin-associated disease of diabetes although it is rare. Prevalence ranges from 0.3 to 1.2% of all diabetics to 2 to 3% in the insulin-dependent subtype and even higher rates in female patients. Patients with Type 1 diabetes develop the disease earlier than those with Type 2 diabetes. Diabetes usually proceeds with the onset of necrobiosis lipoidica by 10 years although simultaneous and reverse patterns can be seen [56]. The association is less strong if the skin disease presents on other body parts than the legs. Whether the severity of diabetes and the activity of necrobiosis lipoidica are correlated is still uncertain. Its presence is worth mentioning given the higher prevalence of retino- and nephropathy. Histology shows a dermal infiltrate which usually affects the entire thickness of the dermis. The infiltrate tends to be horizontally orientated showing intervening layers of granulomatous inflammation and horizontal layers of necrobiosis (sandwich), in areas showing palisading of histiocytes surrounding necrobiosis. The deep dermis often shows admixture with lymphocytes and plasmacells (Fig. 61.13). Whether microangiopathy, neuropathy, trauma, immunoglobulin deposition causing vasculitis or a combination of these forms the origin of the collagen matrix destruction is still under discussion. Necrobiosis lipoidica is very

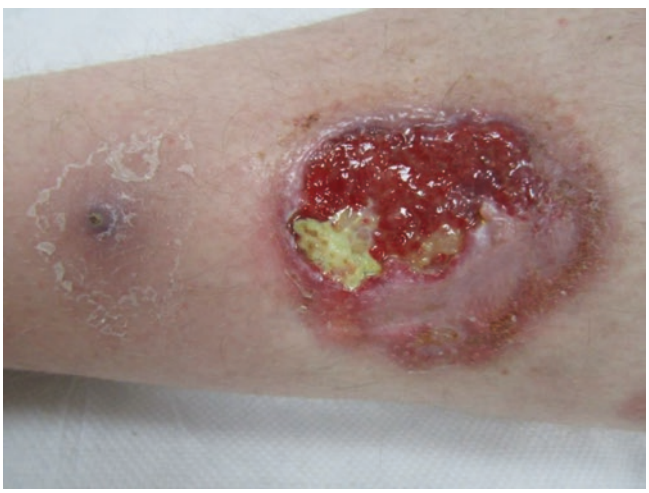

Fig. 61.12 Necrobiosis lipoidica

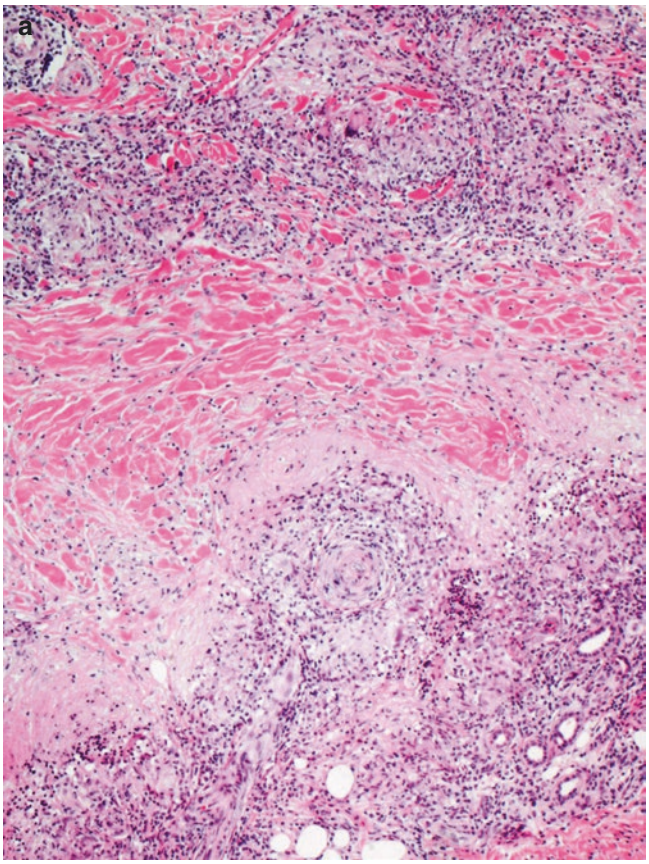

Fig. 61.13 Necrobios lipoidica. The infiltrate shows horizontal "sandwich" layering of (**a**) granulomatous inflammation and necrobiosis (**b**) and fibrosis. The deep dermis often shows a surrounding lymphocytic infiltrate admixed with plasmacells (**c**).

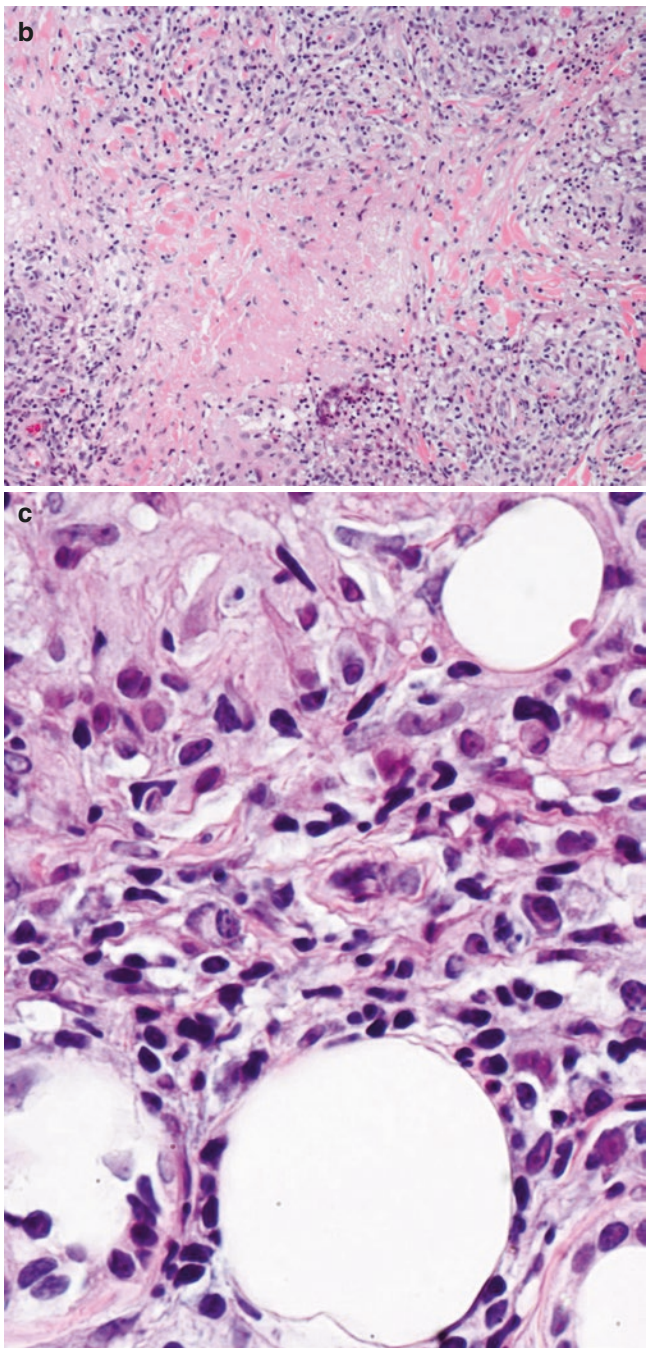

Fig. 61.13 (continued)

hard to treat, but sometimes slow healing occurs. No positive effect of glycemic control has been demonstrated so far [57, 58]. Topical steroids (if necessary under occlusion) are a therapeutic option but can also worsen the atrophy. If an active border is seen, intralesional steroids may be of help. Topical calcineurin inhibitors and compression therapy might be effective. Systemic treatment is possible with chloroquine, fumaric acid ester derivatives, mycophenolate mofetil, cyclosporine, anti-TNF alpha, and psoralen with ultraviolet A radiation (PUVA). Lesions tend to relapse with therapy cessation. Spontaneous resolution is seen in 13–19% of patients after 6 to 12 years [42].

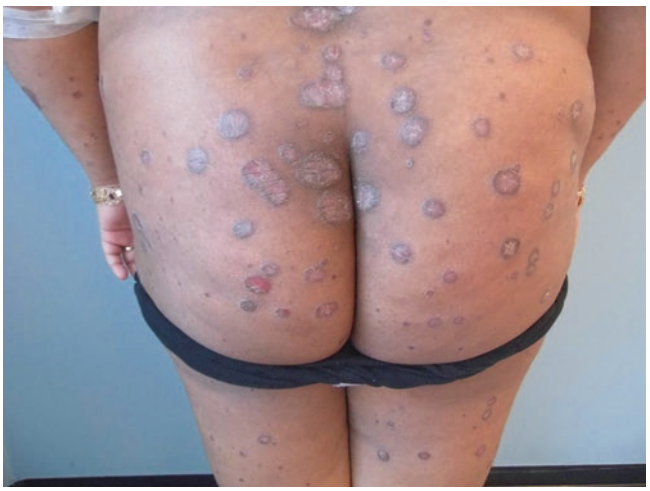

Fig. 61.14 Psoriasis vulgaris

Psoriasis Vulgaris

Psoriasis (Fig. 61.14) is a chronic immune-mediated inflammatory disease of the skin. Patients present with erythematous scaly papules and plaques occurring most frequently in areas of friction [53]. It is common; the prevalence worldwide is estimated to be 1–3% [59]. Association between these two diseases has been made but up until now no consensus was made. Patients with diabetes may present with a more edematous inflammatory course of psoriasis as well as more therapy-resistant psoriasis [60]. Treatment consists of topical (e.g., calcipotriol, corticosteroids, and tacrolimus) or systemic immunomodelators, as well as UV light [53].

Pruritus, Xerosis Cutis, and Keratosis Pilaris

Xerosis cutis, xeroderma, or dry skin is one of the earliest and most frequent skin signs in diabetes, found in almost half the diabetic population. Dry mucous membranes, for example laryngitis scleroticans sicca can be observed as well. Xerosis can be demonstrated in diabetics by measuring transipedermal water loss and high frequency conductance of the forearm [54]. We should keep in mind that both xerosis cutis and diabetes mellitus are very common. The presence of xerosis cutis increases the risk of complications, including infection and ulceration [53]. Pruritus is the main complaint patients present with. In atopic patients, the prevalence of xerosis cutis is higher.

Xerosis cutis is believed to result from sympathetic and sensory neuropathy and also vasculopathy. Sweat gland dysfunction starts with thermoregulatory dysfunction of the extremities and later on the entire body (global anhidrosis), although the reverse can occur (e.g., postprandial gustatory sweating on the face, neck, and chest). Chronic generalized pruritus can be a sign of undiagnosed diabetes as well as truncal pruritus, burning feet syndrome, pruritus vulvae, and anogenital pruritus although the latter may be secondary to candidiasis or streptococci infection. Clinicians should keep in mind that underlying illness and drug reactions also cause pruritus. Regular use of emollients helps to prevent this skin problem.

Keratosis pilaris consists of rough follicular papules and variable erythema on the extensor surfaces of the extremities and sometimes on the face, buttocks, and trunk. It flares up in wintertime. 11.7% of children with Type 1 diabetes have keratosis pilaris but it is very common in non-diabetic patients as well. Xerosis cutis certainly plays a role in this disease. Treatment is difficult and not strictly necessary but emollients as well as keratolytic agents, retinoids, and topical corticosteroids of low potency can be helpful.

Rubeosis Faciei—Palmar Erythema and Periungual Telangiectasia

Acral erythema is an erysipelas-like erythema of the hands (especially the thenar and hypothenar region) and feet and has a mostly patchy distribution due to microangiopathy [61]. It differs from physiological erythema caused by warmth, emotional state, hand elevation, and external pressure in its distribution and aspect of the erythema.

Rubeosis faciei is a relatively common chronic flushed appearance of the face, neck, and upper extremities. It is more easily to notice in Fitzpatrick skin types one and two.

These two asymptomatic skin signs both result from small vessel occlusive disease with compensatory hyperemia of superficial blood vessels or from decreased vascular tone. Described prevalence in patients with Type 1 and 2 diabetes range from less than 10% to over 60% [62–65]. This might be due to confounding factors such as Fitzpatrick skin type [66], severity of disease, and inpatient status. It is associated with vessel engorgement which contributes to visual impairment in diabetics. The erythema (Fig. 61.15) is directly related to disease duration. Improvement is seen with adequate control of blood sugar levels but these phenomena flare up with concomitant use of vasodilating therapies or vasodilators such as caffeine and alcohol.

Periungual telangiectasia are clinically visible dilated capillary veins due to loss of capillary loops and dilation of other surrounding capillaries. It is seen in 40–50% of all patients with diabetes. It can also be seen in connective tissue diseases such as scleredema and dermatomyositis. It is highly likely that nail folds show erythema and that cuticles are ragged (this should not be confused with paronychia caused by infection). Some patients are asymptomatic while others experience discomfort in their fingertips. No treatment is necessary [53].

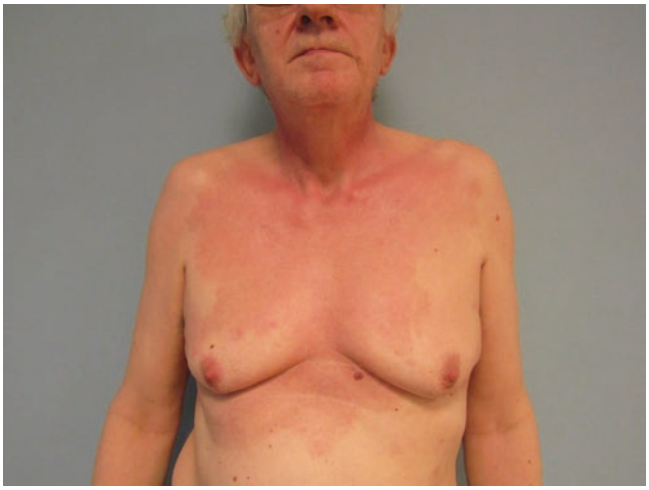

Fig. 61.15 Erythema

Different skin types are divided based on skin color and response to ultraviolet irradiation.

Skin Thickening and Scleredema Diabeticorum

Skin thickening and scleredema diabeticorum are associated with long-term disease progression and diabetic neuropathy ($P < 0.05$) [67] and is a cutaneous marker for other microvascular complications.

There are three subtypes of skin thickening. In the first subtype, there is a benign asymptomatic thickening which is only measurable with ultrasonography. This type is seen in nearly 25% of all diabetic patients. The second type of skin thickening is clinically noticeable. Phenotypes range from Huntley papules to diabetic hand syndrome in 8 to 50% of diabetic patients [68, 69]. The initial complaints in diabetic hand syndrome consist of stiffness and progresses to limited joint mobility and possibly Dupuytren contracture (caused by shortening of skin anchoring ligaments).

Scleredema diabeticorum is a rare asymptomatic diffuse ill-defined erythematous induration of the upper back and neck possibly extending to the deltoid and lumbar region. Acral regions are spared. The skin can have a peau d'orange aspect. Reduced elasticity of the skin can result in reduced joint mobility, and thus stiffness frequently coexists. Two-and-a- half to 14% of patients with diabetes suffer from this condition. Men and obese patients with long lasting Type 2 diabetes are at higher risk. Pathology reports show an unaf-

fected epidermis and a homogenous thickened dermis with activated fibroblasts and enlarged collagen bundles separated by mucin deposition. It is important to take a full thickness excisional biopsy. An excess of blood glucose leads to collagen synthesis by fibroblasts and retarded collagen degradation and glycosaminoglycan depositions. Scleredema is also seen in rheumatoid arthritis, hyperparathyroidism, Sjögren's syndrome, and seldom in IgG paraproteinemia or malignancy.

Scleredema diabeticorum and classic scleredema are clinically difficult to distinguish but appear to have distinct light and electron microscopic features [70]. Scleredema diabeticorum does not improve with glycemic control although this measure is believed to be an important preventive tool. Treatment is often difficult and includes UVA (psoralen UVA as well as UVA1) and systemic therapy such as oral corticosteroids, cyclosporine, cyclophosphamide. In severe cases, radiotherapy could give some relief [71–74].

Ulcers

see Chap. 65, foot complications.

Vitiligo

In vitiligo (Fig. 61.16), depigmented maculae are seen which are slowly progressive. The extent of affected skin ranges from localized to generalized and even universal and is mostly seen on the face, hands, and genitals. Histopathology shows the absence of melanocytes in the basal layer after Melan A staining (Figs. 61.17 and 61.18). It is possible that some melanocytes are seen around the hair follicles. The depigmentation is the result of immune mediated melanocyte loss or function loss, and tyrosinase is the main antigen recognized. One in three patients has a positive family history of vitiligo. One to 7% of insulin-dependent diabetics suffers from vitiligo [2] compared to a 0.2 to 1% prevalence in the global population making it the most common depigmenting disorder [5]. Due to the high number of Type 2 diabetics, these patients will be seen more often with vitiligo,

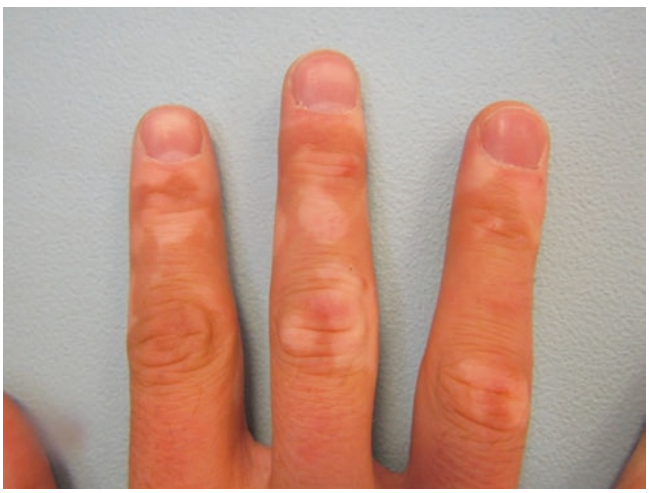

Fig. 61.16 Vitiligo

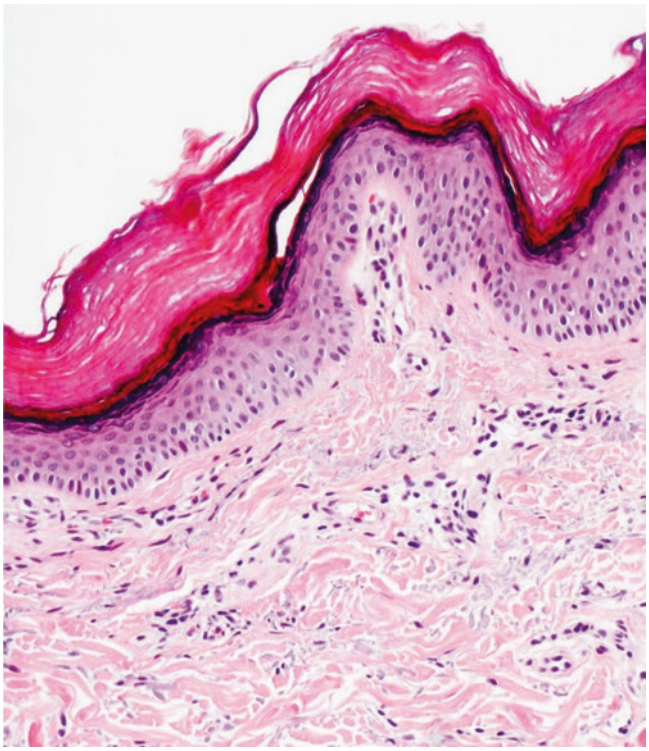

Fig. 61.17 Vitiligo. Absence of melanocytes (HE stain)

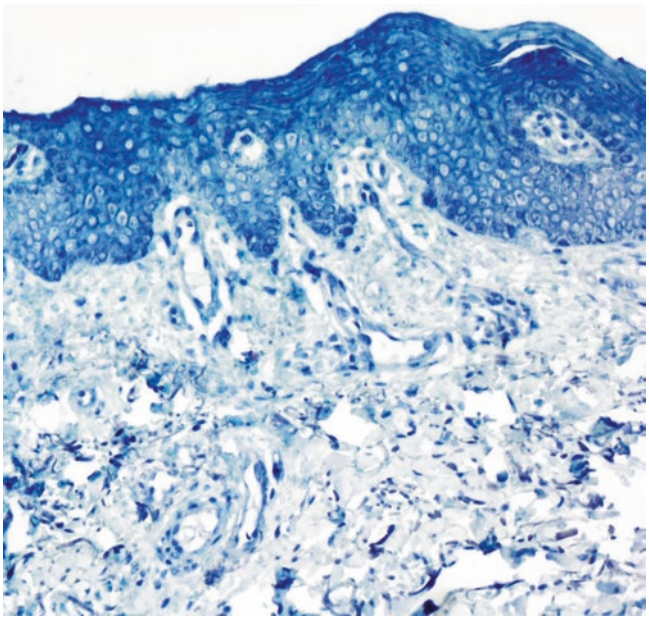

Fig. 61.18 Vitiligo. Absence of melanocytes (Melan A stain)

though it is relatively more prevalent in Type 1 diabetes. The combination of Type 1 diabetes and vitiligo is suggestive for polyglandular autoimmune syndrome. This is a rare immune-mediated endocrinopathy with at least two affected endocrine glands. In these cases, vitiligo is often more difficult to treat. Patients should avoid sun exposure. Topical corticosteroids of high potency can give satisfying results if applied early on (with or without narrow-band ultraviolet B). Topical calcineurin inhibitors have shown some benefit. PUVA and 8-methoxypsoralen lotion can be used as well. In generalized vitiligo, treatment with ultraviolet B light may be an option as well. Camouflage therapy is an option if patients have cosmetic concerns.

Yellow Skin

The yellow skin of some diabetic patients consists of an orange to yellow discoloration of the skin, most obvious on the palms and soles. The sclerae are spared in contrast to patients suffering from jaundice. Yellow nails (Fig. 61.19) affects up to 40% of diabetic patients, especially the elderly. The yellow color is best visible at the distal part of the nails, and these discolored nails have a slower growth rate and appear more curved due to poor vascularization of the nail matrix. Differential diagnosis includes physiological processes in the elderly, onychomycosis, yellow nail syndrome, yellow nails due to lymphedema or respiratory tract disease [75].

The relationship of both discolorations to diabetes mellitus is questionable. Some believe that diabetic patients are exposed to higher levels of carotene in their diet rich of fruits and vegetables, which together with an impaired hepatic conversion leads to carotenemia and thus yellow discoloration of skin and nails. Differential diagnosis of carotenemia includes jaundice hypothyroidism, hypogonadism, hypopituitarism, bulimia and anorexia nervosa [13].

Another possibility is the formation of advanced glycation end products, especially 2-(2-furoyl)-4[5]-(2-furanyl)-1H-imidazole, which has a yellow hue as mentioned earlier. There is currently no treatment available.

Mucormycosis

Mucormycosis is a rare opportunistic fungal infection, with a high mortality rate, caused by fungal species belonging to the order Mucorales (class Zygomycetes). Mucormycosis occurs in immunocompromised patients. Risk factors include poorly controlled diabetes mellitus, end-stage renal disease, hematologic malignancies, and solid organ transplantation. It can affect various organs, including sinuses, nose, eyes, brain, intestine, lungs, and skin. Clinical presentation depends on the anatomical site of involvement, which is associated with the predisposing medical condition. Diabetes mellitus, for example, was found to be correlated with rhinocerebral mucormycosis [76]. In the skin, it presents as an indurated plaque which rapidly evolves into a necrotic ulcer. The diagnosis can be confirmed by histological evalution; broad non-septate hyphae can be observed in blood vessels (Fig. 61.20).

Whilst mucormycosis is prevalent globally, the disease is most common in India [77]. Lately, higher infection rates have been reported worldwide in COVID-19 patients [78, 79]. The exact incidence and prevalence remain unknown. Treatment of mucormycosis is difficult, as mucorales are naturally resistant to most antifungals. Amphotericin B and surgical debridement or excision are the most effective options [78].

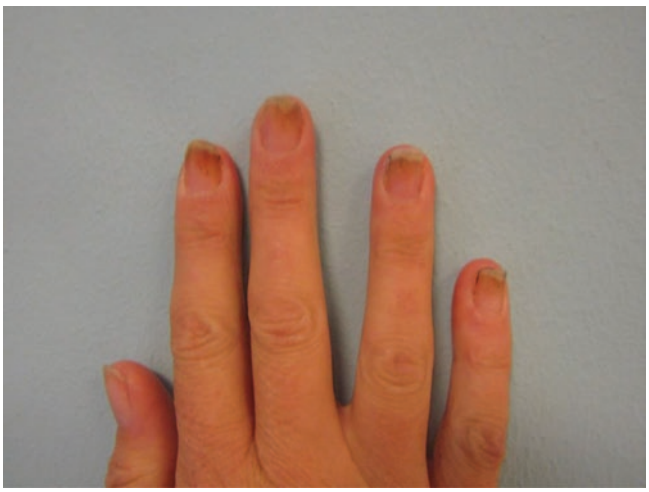

Fig. 61.19 Yellow nails

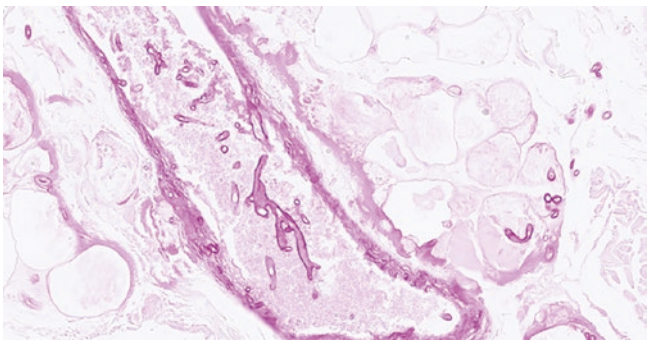

Fig. 61.20 Mucormycosis: Broad non-septate hyphae in a vascular lumen and wall. PAS+ stain

Necrotising Fasciitis

Necrotising fasciitis is a bacterial infection, localised in any of the layers within the soft tissue compartment (dermis, subcutaneous fat tissue, superficial fascia, deep fascia, or muscle). It is a rapidly progressive disease with a high mortality rate. Early recognition, surgical treatment (amputation, fasciotomy, and debridement of necrotic tissue), plus intravenous antibiotic therapy, and hemodynamic support are the most important factors effecting survival rate [80, 81]. Patients usually present with pain disproportionate to clinical signs, which may include erythema with poorly defined edges, oedema, and bullae. At a later stage, purpura and necrotic tissue may be present. Furthermore, patients can present with signs of sepsis, such as hypotension, tachycardia, and fever [81, 82]. Microscopically an extensive diffuse neutrophilic infiltrate can be seen in the subcutaneous fat tissue (Fig. 61.21a, b). However, necrotising fasciitis is a clinical diagnosis.

Necrotising fasciitis may result from any skin damage (i.e., minor trauma, skin biopsy, laceration, insect bite, needle puncture [particularly intravenous drug use], chronic ulcer, herpes zoster, surgical wound, skin abscess). Diabetes mellitus is the most common co-morbidity associated with necrotising fasciitis. A possible explanation why patients with diabetes are more prone to necrotizing fasciitis is that peripheral sensory polyneuropathy increases susceptibility to minor trauma. Next to this, tissue hypoxia caused by vasculopathy and the underlying immunodeficiency in diabetic patients may ease out bacterial colonization [83]. Other predisposing factors include use of immunosuppressants, malnutrition, and peripheral arterial disease [3]. COVID-19 can be an aggravating factor [84].

COVID-19, the Skin, and Diabetes

COVID-19, caused by the novel coronavirus SARS-CoV-2, is most notorious for causing respiratory pathology. However, multiple extrapulmonary manifestations have been described, among which is skin manifestations. Erythematous rash, chil-

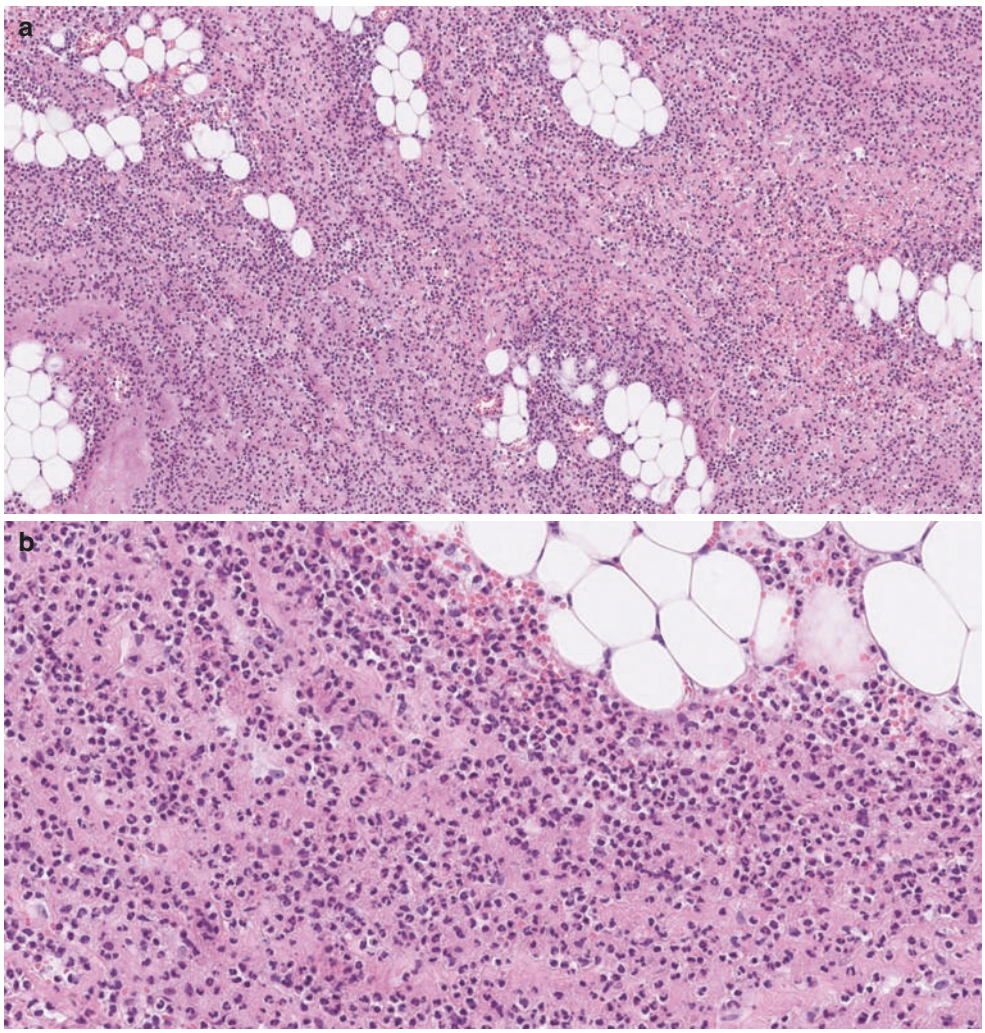

Fig. 61.21 (**a**) (Magnification 10×)—necrotising fasciitis: An extensive and almost pure diffuse neutrophilic infiltrate in the subcutaneous fat. (**b**) (Magnification 40×)—necrotising fasciitis: An extensive and almost pure diffuse neutrophilic infiltrate in the subcutaneous fat

blain-like lesions, and urticarial lesions were most commonly reported [85, 86]. Other manifestations include exanthema in various forms (morbilliform/maculopapular/papulovesicular), livedoid/necrotic lesions, and purpura/petechiae. The skin lesions were often accompanied by pruritus and were mostly self-resolving [83–87]. SARS-CoV-2 enters the human cells via the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in various organs, including the skin. Especially, keratinocytes in the epidermis show a high expression of ACE2, which can explain the presence of cutaneous manifestations in COVID-19 patients [85, 88].

Diabetes mellitus is one of the comorbidities associated with COVID-19, and diabetic patients are at risk of developing a more severe disease manifestation. Hyperglycemia and ketosis, as a result of deterioration in pancreatic β-cell function and apoptosis, caused by elevated cytokine levels, are mechanisms that may account for the more severe disease course. Next to this, the presence of ACE2 receptors in the pancreas might contribute to insulin deficiency and hyperglycemia. Consequently, COVID-19 can be associated with deterioration of skin manifestations of diabetes mellitus [88, 89].

Side Effects of Medication

Side Effects of Insulin

Insulin Lipodystrophy.

Atrophy and hypertrophy of the skin might both occur although they are less frequently seen since the use of more pure insulins and synthetic analogues. Hypertrophy used to be present in two-thirds of insulin-dependent patients, but this number has been reduced to 1 to 2 %. It is characterized by a localized hypertrophy of subcutaneous fat. In these hypertrophic areas, insulin absorption is delayed; therefore, patients should rotate the injection site. Hypertrophy resolves spontaneously.

Atrophy at the insulin injection sites is due to an immunological reaction including IgM, IgE, and C3 in dermal blood vessels initiating a signal cascade that inhibits adipocyte differentiation [90]. Duration of exposure and depot formation play a role in the onset of atrophy. Substitution with fast acting insulin has been suggested as therapy [3]. It is unknown why women are more likely to develop atrophy and why men suffer from lipohypertrophy more often.

Continuous subcutaneous insulin infusion with the latest types of infusion materials does not frequently induce local infections, although allergy to tape and certain tubing constituents can be seen.

Allergic reactions to insulin are seen in approximately 2.4% of insulin-dependent diabetics. They can be classified into four categories (immediate local, generalized, delayed, and biphasic). Immediate local reactions range from erythema to urticaria and are assumed to be IgE mediated. Peak intensity is reached in 15–30 min and resolves within an hour. The immediate local reaction may progress to generalized erythema and urticaria. Anaphylaxis is rare. Delayed forms (4–24 h after injection appearing 2 weeks after the start with insulin therapy [3, 11]) present most frequently with itchy nodules at the injection site. Biphasic reactions are rare and consist of a combination of an immediate and a delayed local reaction in patients with symptoms resembling serum sickness. Treatment with topical corticosteroids is almost always successful.

Oral Hypoglycemic Medication

A wide range of quit frequently appearing cutaneous drug reactions to oral antidiabetic agents have been described ranging from pruritus, photosensitivity, allergic reactions, erythema multiforme, erythema nodosum, urticarial and pruritus to lichenoid, and morbilliform eruptions.

- Sulphonylurea has the most skin-related side effects, as approximately 1 to 5% of patients develop cutaneous reactions within 2 months of treatment. Maculopapular eruptions are the most common. Other cutaneous side effects include erythema, urticaria, erythema multiforme, exfoliative dermatitis, erythema nodusum, pemphigus vulgaris, psoriasiform, and lichenoid drug eruptions. Most sulfonylureas can induce photosensitivity. Even with a negative patch test, oral antidiabetic therapies should be switched.
- Approximately 20 % develop an alcohol flush with symptoms of redness, warmth, headache, tachycardia, and seldom dyspnea within 15 min after alcohol consumption and disappearing within the hour. Second- generation sulphonylureas present with less cutaneous side effects.
- Meglinitinides or glinides rarely cause cutaneous reactions (<0.01%). If present, they usually consist of pruritus, rash, urticarial, or generalized reactions such as anaphylaxic shock.
- Biguanides such as metformin cause cutaneous side effects ranging from psoriasiform drug eruptions and leucocytoclastic vasculitis to phototoxic reactions and erythema multiforme.
- Thiazolidinediones glitazones can seldom cause edema.
- Dipeptidyl peptidase IV inhibitors give dose-dependent necrotic skin lesions in monkeys. Increased rates of angioedema are noted only if they are used together with ace inhibitors due to inhibition of the degradation of bradykinin and substance P. Case reports show severe skin reactions such as bullous pemphigoid, Stevens–Johnson syndrome and toxic epidermal necrosis.

– Alpha glucosidase inhibitors-like acarbose have been responsible for acute generalized exanthematous pustulosis and erythema multiforme.
– Injection of Glucagon-like-peptide-1 receptor agonist (or incretinomimetics) can cause local granulomatous reactions (e.g., eosinophilic sclerosing lipogranulomas).

Concluding Remarks

The skin is often involved in diabetes mellitus as well as in side effects of medications used to treat diabetes. Some of those skin diseases are more specific for diabetes than others and some are more frequent in Type 1, others in Type 2 or both types of diabetes mellitus.

The intensity ranges from mild to severe. Recognizing these skin conditions may be of great value since they can be the presenting symptom in diabetes mellitus, port of entry for infection, or sign of advanced disease.

Multiple Choice Questions

1. Which statement is false?
   A. **A Circa 10% of all patients with diabetes mellitus develop skin manifestations.**
      False, 30–80% of all patients with diabetes mellitus develop skin manifestations.
   B. Patients care a lot about the appearance of their skin.
   C. Disseminated granuloma annulare can be observed in diabetes mellitus patients, malignancies, thyroid dysfunction, hepatitis B, C, and HIV infections.
   D. Skin manifestations of diabetes mellitus can be present before the diagnosis of diabetes mellitus.
   E. Some of the skin manifestations of diabetes mellitus are linked to neuropathy and angiopathy.
2. What is true about acanthosis nigricans?
   A. Acanthosis nigricans can only occur in patients with diabetes mellitus.
   B. Acanthosis nigricans is highly disabling.
   C. **Acanthosis nigricans occurs in the intertriginous areas.**
      Correct, especially in the neck, armpits, and groins.
   D. After treatment no recurrence is possible.
   E. It occurs more often in the Caucasian race.
3. Acquired perforating dermatosis is (Fig. 60.22).
   A. easy to treat.
   B. a frequently appearing dermatosis.
   C. is most frequently seen on the flexor areas of the lower extremities.
   D. **a highly pruritic skin disease.**

Correct. It presents with scaly highly pruritic follicular hyperkeratotic papules and nodules.

   E. more frequently seen in Caucasian people.
4. Which statement about bullosis diabeticorum is false?
   A. There are three known subtypes.
   B. **all subtypes heal without scarring.**
      False, the cleavage level of the second subtype lies below the dermoepidermal junction so healing leaves scars.
   C. It occurs more frequently in men with longstanding poorly controlled Type 1 diabetes.
   D. No treatment is needed.
   E. Primary autoimmune blistering should be excluded.
5. Diabetic dermopathy is.
   A. **a synonym for shin spots.**
      Correct, these are asymmetric red to brown hyperpigmentated spots.
   B. a synonym for diabetic stiff hands.
   C. no reason to screen for diabetes mellitus.
   D. a skin manifestation that never preceeds to diabetes mellitus.
   E. a unilateral appearing dermatosis.
6. Which statement concerning eruptive xanthomas is false?
   A. A Patients with eruptive xanthomas are usually asymptomatic.
   B. There is a correlation with elevated blood triglycerides.
   C. There is an elevated risk of pancreatitis.
   D. **Systemic treatment is indicated.**
      False, the main treatment objective is controlling the hypertriglyceridemia. Local therapeutics can be used.
   E. 10% of all diabetes mellitus patients develop eruptive xanthomas.
7. Which statement on granuloma annulare is false?
   A. Granuloma annulare is a rare benign inflammatory disease.
   B. This disease usually occurs on the hands and arms.
   C. **All forms occur more frequently in patients with diabetes mellitus.**
      False, only the disseminated form occurs more frequently in diabetes mellitus patients.
   D. It is sometimes histopathologically difficult to distinguish from necrobiosis lipoidica.
   E. Multiple subtypes exist.
8. Which statement on lichen planus is true?
   A. Lichen planus is a chronic inflammatory disease due to overactivity of the B cells.
   B. Lichen planus only occurs on the oral mucous membrane.
   C. The relationship to diabetes mellitus is completely clear.
   D. Lichen planus only occurs on the skin.
   E. **Four Ps can be used as a mnemonic.**

Correct, it stands for pruritic, purple, polygonal, papules, or plaques.

9. What is true about necrobiosis lipoidica?
   A. **A It is important to diagnose.**
      Correct, prevalence of retinopathy and nephropathy is higher in this subgroup of patients.
   B. Never preceeds to diabetes mellitus.
   C. Occurs in the first and second decade.
   D. This skin condition never heals.
   E. This skin condition is easy to treat.
10. Which statement on vitiligo is false?
   A. Patients with vitiligo should avoid sun exposure.
   B. After melan A staining, no melanocytes are observed on histopathological examination.
   C. **It occurs more often in Type 2 diabetes.**
      False, vitiligo occurs more frequently in Type 1 diabetes. Both are auto-immune diseases.
   D. Ultraviolet B light may be of help in the treatment of this disease.
   E. Topical corticosteroids and calcineurin inhibitors are used in the treatment of vitiligo.

Glossary

Atrophy A loss of tissue from the epidermis, dermis, or subcutaneous tissues. There may be fine wrinkling and increased translucency if the process is superficial.

Erythema Redness of the skin produced by vascular congestion or increased perfusion.

Koebner phenomenon The onset of new inflammatory skin lesions after minor trauma such as scratching.

Macula A circumscribed alteration in the color of the skin.

Nodule A solid mass in the skin, which can be observed as an elevation or can be palpated. It is more than 0.5 cm in diameter. It may involve epidermis and dermis, dermis and subcutis, or subcutis alone. It may consist of fluid, other extracellular material (e.g., amyloid), inflammatory, or neoplastic cells.

Papule A circumscribed palpable elevation, less than 0.5 cm in diameter. By careful examination it is often possible to determine whether the thickening involves predominantly the epidermis or the dermis and what type of pathological process is concerned. The only distinction between a papule and a nodule is the size, and this is artificial; some lesions characteristically occur at the smaller size of a papule, whereas others typically enlarge from a papule to become a nodule. Recording a finite size is more useful.

Plaque An elevated area of skin, usually defined as 2 cm or more in diameter. It may be formed by the extension or coalescence of either papules or nodules as in psoriasis and granuloma annulare, respectively. Small plaque is sometimes used for such lesions 0.5–2 cm in diameter.

Sclerosis Diffuse or circumscribed induration of the subcutaneous tissues. It may also involve the dermis, when the overlying epidermis may be atrophic. It is characteristically seen in scleroderma, but may occur as a sequel to or in association with many different processes.

Ulcer A loss of dermis and epidermis, often with loss of the underlying tissues.

Vesicles and bullae Visible accumulation of fluid within or beneath the epidermis. Vesicles are small (less than 0.5 cm in diameter) and often grouped. Bullae, which may be of any size over 0.5 cm, should be subdivided as multilocular (due to coalesced vesicles, typically in eczema) or unilocular [91]

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Foot Complications

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Lawrence B. Harkless, Jarrod Shapiro,
and Joel Rodriguez-Saldana

Introduction

Patient C was a 50-year-old diabetic male truck driver. He presented to the emergency department with a red, hot, painful, swollen right foot and lower leg. There were no open lesions with unilateral edema and diffuse erythema. A venous duplex ultrasound was negative for deep venous thrombosis. Laboratory data showed no leukocytosis. The patient was admitted, placed on broad spectrum I.V. antibiotics, and discharged three days later. He returned to the emergency department 3 days after discharge with the same complaint of persistent redness and swelling. A second venous ultrasound was negative for thrombosis, and he was discharged home with a new oral antibiotic and a referral to the podiatry clinic. After a 2 week delay in obtaining an appointment, the patient noted his right foot had changed shape and was flatter in the arch than the contralateral foot. The deformity progressed to ulceration requiring surgical intervention. This unfortunate outcome in which the correct diagnosis of acute Charcot neuroarthropathy was missed resulted in considerable patient morbidity and increased healthcare utilization.

Diabetic foot complications are serious events in the lives of patients with diabetes. Historically, pedal complications were underappreciated by the general medical community; however, international efforts have improved the recognition of this very serious problem. All health professionals involved with diabetic patients should be well informed about the potential complications of diabetic foot syndrome. This chapter will discuss diabetic foot complications with an emphasis on a conceptual framework of the epidemiology, risk, and wound-healing concepts underlying these complications. A detailed discussion of diabetic foot ulcerations, infections (including skin and soft tissue structure infections and osteomyelitis), Charcot neuroarthropathy, and the role of targeted partial foot amputations will provide healthcare professionals with an understanding of this detrimental disease.

Diabetes is highly common with an estimated 194 million diabetics worldwide [1]. It has also been estimated that 344 million people will be diabetic by 2030 [1]. Of this number of affected people, 15% will develop a diabetic foot ulcer at some time [2], which corresponds to 2% to 6% of diabetics yearly with an estimated 6.9 million that will be affected in 2030 [2]. Diabetes has a significant and often catastrophic effect on patients' lives with global health implications. It is estimated that diabetic patients overall have a 15% risk of lower limb amputation [3]. Of this number, 85% are preceded by an ulcer [2]. Patients who develop an ulcer have a 34% risk of developing another wound within 1 year of healing the index ulcer and a 70% chance at 5 years [4].

Patients often fair poorly with the onset of foot ulceration. Diabetic foot ulcers that progress to lower limb amputation set off a catastrophic chain of events with a 50% risk of contralateral foot ulceration and a 50% rate of contralateral limb amputation within 2 to 5 years [5]. Mortality rates are significantly worsened when considering diabetic foot complications. Five-year mortality rates are 45%, 18%, and 55% for patients with neuropathic, neuroischemic, and ischemic ulcerations, respectively [6]. Limb amputations have similarly dismal survival outcomes. Mayfield et al. reviewed Veterans Affairs discharge documents of 5180 patients who underwent some type of lower limb amputation. They found a 56% 5-year mortality rate after transtibial and 70% mortality after transfemoral amputation [7]. Hoffman et al. found similar poor prognoses after major limb amputation with 1,3,5, and 10-year survival rates of 78%, 61%, 44%, and 19%, respectively [8].

The addition of Charcot neuroarthropathy worsens yet the prognosis of these patients. Sohn et al. found a 59% incidence of foot ulceration in those with Charcot foot (538 of

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911 patients). Of these, 66% were treated for foot ulcer at the time of Charcot diagnosis [9]. They also found the relative risk of amputation for patients with foot ulcer and Charcot was 12 times higher than those with Charcot alone [9].

The cost of diabetic foot complications may also be catastrophic. Ramsey et al. retrospectively reviewed 8905 patients from a health maintenance organization and found the cost for a 40- to 65-year-old diabetic male with a new foot ulcer in 1999 was $27,987 over a 2-year period [2]. With inflation, this corresponds in 2016 to $40,003 [10].

These figures demand a specific set of conclusions. The first is that the majority of diabetic foot ulcers and major limb amputations are preventable. When they occur, a foot ulcer greatly increases the risk of further complications such as soft tissue and bone infection and must be treated aggressively. Third, limb amputation is preceded by foot ulceration that becomes secondarily infected with limb amputation as the end result. Finally, the costs associated with diabetic foot complications are extraordinary and place a very large burden on the world's healthcare system.

This has led some to consider how diabetic foot complications compare with other diseases. Armstrong, et al. compared the 5-year mortality rates of neuropathic ulcers and amputations with various types of cancer [6]. They found 5-year mortality rates of neuropathic ulcers and amputations to be equivalent to colon cancer and worse than Hodgkin's disease, breast cancer, and prostate cancer (Fig. 62.1). This has prompted the concept of *malignant diabetes* in which diabetic foot complications are markers for a diabetic process that has advanced to a severity equivalent to (and sometimes worse than) cancer (courtesy Jeff Robbins, DPM, personal communication).

With this background in mind, it is possible to consider a conceptual pathological framework for diabetic foot complications with an emphasis on healing concepts, risk assessment, and psychosocial aspects that play an important role in this process.

At a macroscopic level, the continuum of diabetic foot ulceration to infection to amputation is clearly understood. The hyperglycemic process leads to peripheral neuropathy (discussed below) and loss of large and small sensory fibers. This loss of protective sensation reduces or eliminates the capacity to sense low-grade repetitive or single high-grade traumatic pressures to specific aspects of the foot. Low-grade microtrauma is mediated by the presence of structural deformity or limited joint motion [11, 12] (Fig. 62.2). As pressures continue to wear away epidermis, deeper layers become exposed creating the neuropathic ulcer. If the ulcer remains exposed, the likelihood to become colonized with opportunistic skin flora with contamination cellulitis and infection is high. Chronic or acute infection may lead to osteomyelitis of the nearby bone with possible amputation.

Treating pedal complications successfully requires an understanding of the normal wound-healing process. Aberrant healing associated with diabetic foot complications is discussed later in this chapter. Initial wound healing begins with the hemostatic inflammatory phase, mediated by neutrophils, which diminish in number after the first 24 h and replaced with macrophages and lymphocytes. The proliferative repair phase occurs between several days after injury to the first few weeks,

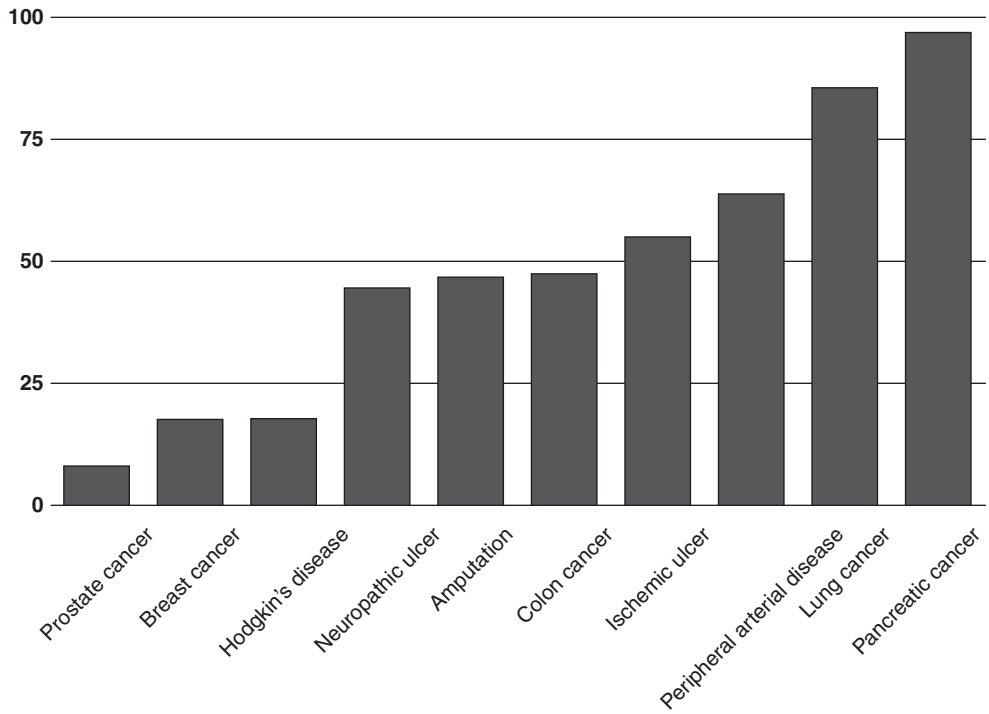

Fig. 62.1 Five-year mortality percentages comparing neuropathic ulceration and amputation with other common malignant diseases (Armstrong et al. with permission)

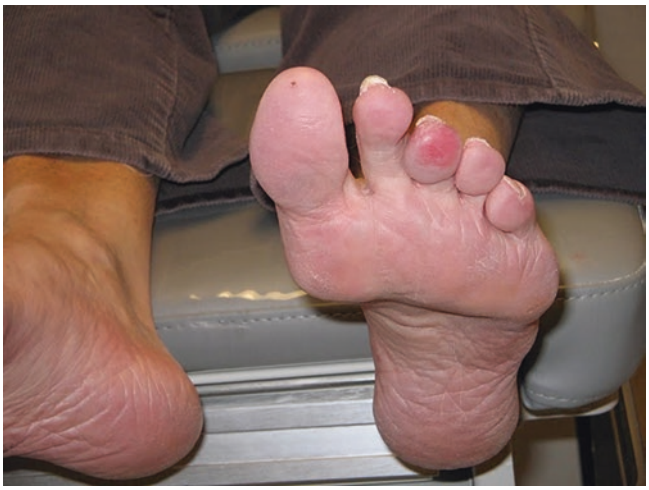

Fig. 62.2 Preulcerative digital erythema due to chronic repetitive low-grade pressures caused by hammertoe deformity

with steadily increasing fibroblasts and endothelial cells. It is at this stage that the typical diabetic foot ulcer healing process stalls. The final phase, remodeling, occurs after several weeks with type 1 collagen replacing the prior epidermal type III collagen, leaving a healed skin surface with approximately 80% of its original tensile strength [13]. During the proliferative phase, three mechanisms occur: connective tissue deposition (described above), contraction (mediated by myofibroblasts), and epithelialization [13]. Each of these phases is mediated by various cytokines and cell signaling pathways. Successfully, healing diabetic foot ulcers will heal by a variable combination of these three methods.

Peripheral vascular disease has a profound effect on the assessment, treatment, and prognosis of diabetic foot complications. Diabetics with peripheral arterial disease (PAD) are at significantly greater risk for poor outcomes. Jude et al. examined the relationship between diabetes and PAD severity and outcomes by examining the lower-extremity angiograms and medical records of 58 patients with diabetes and 78 without. The results of their analysis depicted that patients with diabetes had greater PAD severity in the profunda femoris and all arterial segments below the knee ($P \leq 0.02$). Furthermore, diabetes was associated with a risk for amputation that was five times greater than that for nondiabetic patients (41.4% vs 11.5%, odds ratio [OR] 5.4, $P < 0.0001$) and mortality that was double for nondiabetic patients (51.7% vs. 25.6%, OR 3.1, $P = 0.002$) [14].

When considering the risk spectrum of peripheral arterial disease in the diabetic patient, it is efficacious to consider an organized approach using the patient's medical history. Harkless and Holmes created a vascular risk spectrum from patient historical data [15]. Table 62.1 lists the pertinent components of this risk spectrum. The clinician obtains the appropriate history, including the listed components, and

Table 62.1 Vascular risk spectrum

Risk Type	Historical Component
Macrovascular disease	CAD, CVA/TIA, intermittent claudication
Microvascular disease	Retinopathy, nephropathy, neuropathy
Functional microvascular disease	Gastroparesis, impotence
Metabolic syndrome	Impaired glucose tolerance(IGT) pre diabetes, insulin resistance(IR), HTN, hyperlipidemia, obesity smoking
Family history	History of DM and complications

determines a low, medium, or high risk for the presence of peripheral arterial disease. This system has not been validated but provides the clinician with a basis in which to understand the presence of PAD and order further testing.

Each of the risk components described above cumulatively increases the risk for peripheral arterial disease and an increased chance of poor outcomes when combined with other complications such as neuropathic ulceration, Charcot arthropathy, or infection. The UKPDS trial found for each 1% increase in glycosylated hemoglobin, there was a 28% increase in peripheral arterial disease at 6 years after diagnosis. Additionally, each 10-mmHg increase in systolic blood pressure increased the risk by 25%, and smoking, prior diagnosis of coronary artery disease, and dyslipidemia were also independent risk factors for PAD [16].

The significance of this vascular risk spectrum is compounded by the concept of metabolic memory in which diabetes complications persist and progress after glycemic control is established. The converse of this, in which intensive glycemic control has a prolonged protective effect despite later reversion to conventional therapy, was termed the "legacy effect" after the UKPDS trial [17]. Increasing research evidence demonstrates that microvascular complications such as retinopathy and nephropathy in diabetics may be mediated by epigenetic DNA methylation, thus modifying gene expression [18]. The presence of advanced glycation end products (via cross-linking and irreversibly altering protein function) and oxidative stress (through creation of reactive oxygen species and subsequent tissue damage) have also been implicated [19, 20]. Experimental evidence for this process was noted during the Diabetes Control and Complications Trial (DCCT) [21] in which a continued retinopathy effect was noted in the conventional treatment group despite later enrollment and intensive glycemic treatment during the EDIC trial [22]. This process may be logically extrapolated from retinopathy and nephropathy to peripheral neuropathy since these three complications are intimately linked. Further research needs to delineate the mechanisms and biological effects of metabolic memory as they pertain to peripheral neuropathy and diabetic foot complications.

Diabetic pedal complications are made more challenging by patient psychosocial aspects. Nonadherence to medical instruction is highly common in this population with significant lower extremity effects. Armstrong et al. performed a prospective study of 20 diabetic patients with plantar ulcers. They placed a pedometer on the hip and in a removable cast boot and tracked ambulatory activity. Only 28% of walking activities at home were performed while wearing the removable cast boot, and the highest utilizers were the boot only 60% of the time [23]. In a similar study, patients were prescribed prescription shoes with a pedometer to track usage to prevent ulceration. Eighty-five percent of patients wore the shoes outside the home, but only 15% wore them when inside the home, which correlated with more steps per day out of the shoes [24]. Additionally, other studies have demonstrated improved ulcer healing outcomes when protocols were utilized that eliminated the chance of noncompliance [25–28].

Charcot Neuroarthropathy

Charcot neuroarthropathy is a well-documented but poorly understood catastrophic imbalanced inflammatory reaction that occurs most often in the diabetic population in developed countries. This disorder was originally described in patients with tertiary neurosyphilis and knee joint destruction and has generally poor outcomes if not recognized early and treated properly [29–31].

Charcot arthopathy appears clinically as a mild to moderately painful joint destructive disease, but at the molecular level, it has been hypothesized as due to an imbalance in pro-inflammatory cytokines responsible for bone growth regulation [32]. Jeffcoate et al. offer the most current description of this disorder as being initiated by an insult to the foot or ankle which then stimulates osteoclast formation by activating nuclear transcription factor **κ**B (NF-**κ**B) which leads to a significant osteoclastic and lytic process with subsequent bone destruction. This molecule is itself activated by receptor activator of NF-**κ**B ligand (RANKL) and has been implicated as an etiologic factor of blood vessel tunica media calcification [33]. Further research will help elucidate this process and will likely lead to medications that will reduce the effects of this devastating disease.

Clinically, Charcot arthropathy presents in two forms [32] acute and [33] chronic. In the acute phase, the affected foot or ankle presents most commonly with moderate to severe edema, erythema, calor, and variable pain. Patients will present a variable history with or without a known traumatic episode. Due to peripheral neuropathy with loss of sensation, diabetic patients may feel limited pain in comparison to a fully sensate person and may have no recollection of trauma. A low-grade chronic trauma or a more significant injury may be the inciting event.

Charcot arthropathy in which no ulcerations are present create a diagnostic dilemma. One must consider the broad differential diagnosis of an erythematous, edematous foot, including acute gouty arthropathy, cellulitis, osteomyelitis, occult or overt trauma, and deep venous thrombosis. This clinical dilemma may be difficult for the physician to sort out and is best handled with emergent referral of a lower extremity specialist. The index of suspicion for each of these differentials may be lowered with appropriate laboratory and imaging studies. However, one must maintain a high index of suspicion for osteomyelitis in a patient with this presentation. Cellulitis and osteomyelitis may be ruled out based on the understanding that the vast majority of foot infections occur via contiguous spread infection (skin surface bacteria entering the deeper tissues through a breach in the skin) rather than hematogenously. Hematogenous spread osteomyelitis in the diabetic foot is an extremely rare occurrence. However, we have seen several patients with bacteremia seed a Charcot joint. A search of the literature demonstrates no case studies of hematogenous spread osteomyelitis to the diabetic foot. This may be due in part to the smaller number of long bones in the foot and lack of open growth plates as is found in the more common pediatric hematogenous osteomyelitis of the tibia and femur. In cases where there is ulceration with Charcot changes, ruling out osteomyelitis becomes much more difficult.

A careful physical examination should be undertaken, looking for any open lesions in the typically edematous, erythematous foot with warmth and variable pain to palpation [30]. Early stages may show no morphological changes to foot structure, however later in the disease, after joint destruction has occurred, the classic rocker-bottom foot is easily witnessed (Figs. 62.3, 62.4, and 62.5). Charcot arthropathy may occur at any joint of the foot and ankle;

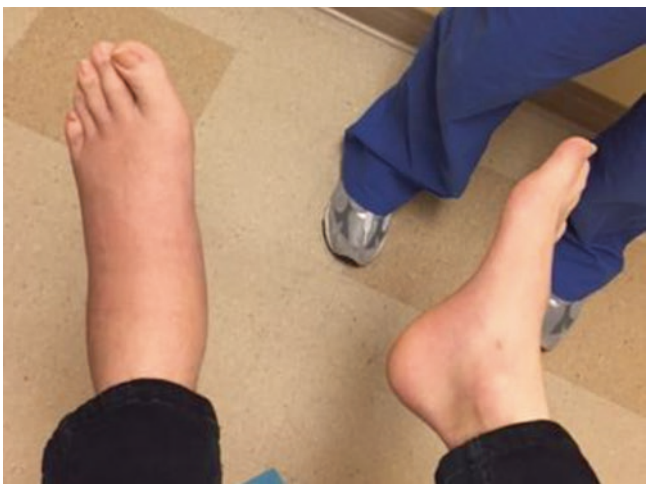

Fig. 62.3 Acute Charcot left foot. Note the edema and subtle erythema. The left foot was warmer than the right. Radiographs at this stage were negative for joint destruction or dislocation

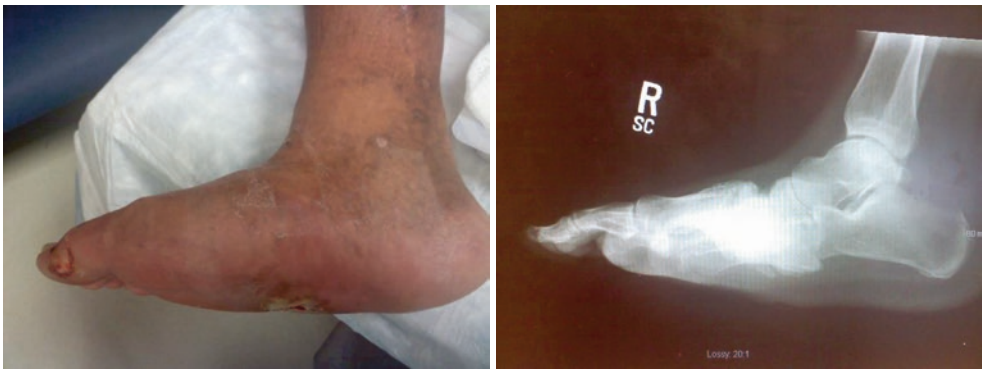

Fig. 62.4 Classic rocker bottom foot deformity secondary to Charcot midfoot collapse. Radiograph of same patient demonstrating Lisfranc and naviculocuneiform collapse

however, the tarsometatarsal joint is most commonly involved. Though slightly less common, ankle Charcot is potentially devastating in its poor outcomes [29].

Temperature differences have been shown to assist with diagnosis of Charcot arthropathy and monitor resolution of the acute phase. A greater than 2 °C temperature difference using an infrared dermal thermometer is helpful in diagnosing acute Charcot and in monitoring progression out of the acute and into the coalescence phase [34, 35]. Thermometry should be used 15 min after cast and dressings are removed, and the thermometer should be accurate to ±0.1 °C [36].

Laboratory studies are often inconclusive with either a demonstrable leukocytosis and elevated nonspecific inflammatory markers, such as erythrocyte sedimentary rate (ESR) and C-reactive protein (CRP), or these values may also be found to be in the normal reference range [34, 37]. It has been shown that the acute local inflammation is dissociated from the systemic inflammatory response in these patients [34], and this lack of a systemic response may help providers in differentiating this disorder from infection. Other laboratory values may demonstrate elevations in glycemic indicators and renal dysfunction. No definitive validated laboratory markers for the specific diagnosis of Charcot neuroarthropathy exist outside of limited research studies.

Typical imaging studies begin with foot and/or ankle radiographs depending on the suspected joint involvement. During the earliest stages of Charcot, radiographs may demonstrate no abnormal findings other than increased soft tissue density and volume. Later stages will be clearly evident on plain film radiographs with joint destruction, fragmentation, dislocation (during the development phase) and progressive sclerosis, ankylosis, and rounding of bone fragments (during the coalescence and remodeling phases) (Figs. 62.6 and 62.7).

Charcot neuroarthopathy of the foot progresses through four primary stages that blend intimately making it difficult to determine if a patient has progressed to the next stage. The modified Eichenholtz classification [38, 39] is most commonly used to stage the disorder. Stage 0 is the most acute (inflammatory) stage with the classic "red, hot, and swollen" appearance. Radiographs are the most often utilized initial imaging modality [40] and commonly show no joint destructive changes in the earliest stage. Stage 1 is the development phase, which also appears as a foot with warmth, erythema, and variable edema. Radiographs may show early mild destruction and joint diastasis. Stage 2 is the coalescence phase in which the inflammatory process subsides with clinical normalization and radiographic changes that appear more chronic in nature with sclerosis of prior lucent bone and a blunting or smoothed appearance to bony fragments. The final third stage is termed remodeling which demonstrates a more chronic appearance similar to stage 2. The timeline of each of these stages vary.

An anatomic classification has also been proposed by Sanders and Frykberg [41]. They defined the location of the Charcot destruction coupled with the frequency of complications as follows:

Pattern I: Forefoot = 15%.
Pattern II: Tarsometatarsal joint = 40%.
Pattern III: Naviculo-cuneiform, Talo-navicular, Calcaneo-cuboid joints = 30%.
Pattern IV: Ankle and/or subtalar joint = 10%.
Pattern V: Calcaneus = 5%.

Other imaging modalities, though useful for other pathologic entities, do not provide significant diagnostic assistance. Computed tomography may assist with diagnosing early nondisplaced fractures [40]. Magnetic resonance imaging (MRI) in most cases is not necessary and may in fact create a diagnostic dilemma. Joint fragmentation, fracture, and bone marrow edema involving multiple joints, the typical Charcot appearance on MRI, may be difficult to differentiate from osteomyelitis, acute exacerbations of chronic osteoarthritis, or gouty arthropathy. In situations where ulceration is present, radiologists will be unable to rule out osteomyelitis. Bone scintigraphy should be avoided due to its lack of specificity [42]. Any inflammatory condition may appear as increased radiotracer uptake, even on delayed phases and white blood cell labeled studies. The reader is cautioned to take careful

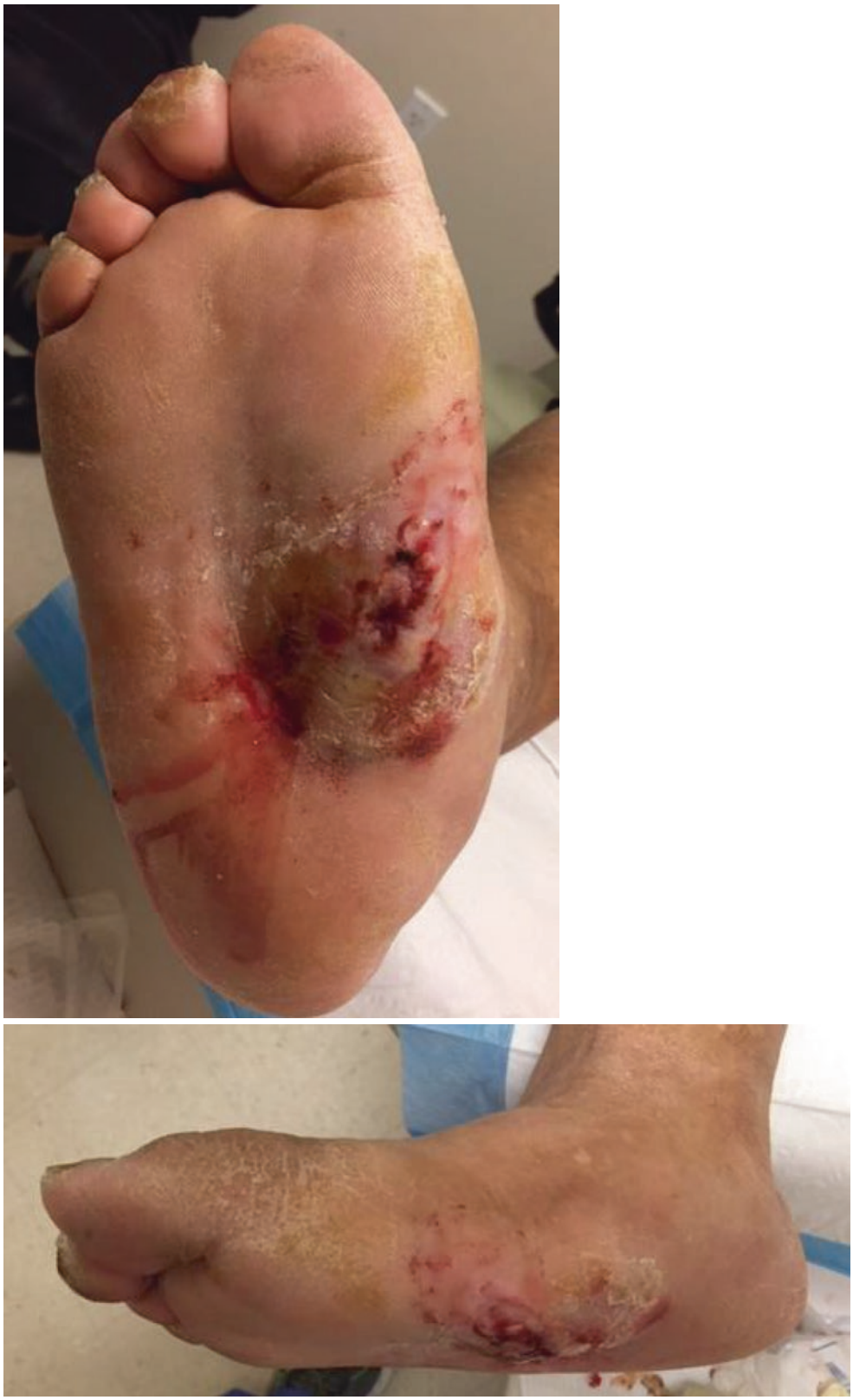

Fig. 62.5 Chronic Charcot of the right midfoot with collapse and rocker bottom appearance. Note the medial arch ulceration due to increased focal plantar pressures

consideration of the results for all advanced imaging studies for the diagnosis of Charcot neuroarthropathy.

Treatment of the Charcot foot varies based on the acuity of the presentation. Acute Charcot arthropathy management consists of stabilization of any comorbid disorders such as establishing appropriate glycemic control, hydration, and intravenous antimicrobials if infection is suspected. Additionally, local wound care is important if ulceration is identified concurrently with arthropathy. Sharp debridement removes bacterial contamination, while most wound care must

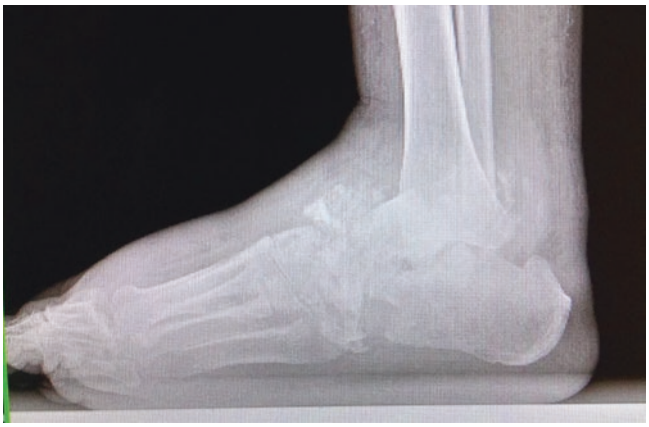

Fig. 62.6 Acute Charcot arthropathy involving the midtarsal and subtalar joints

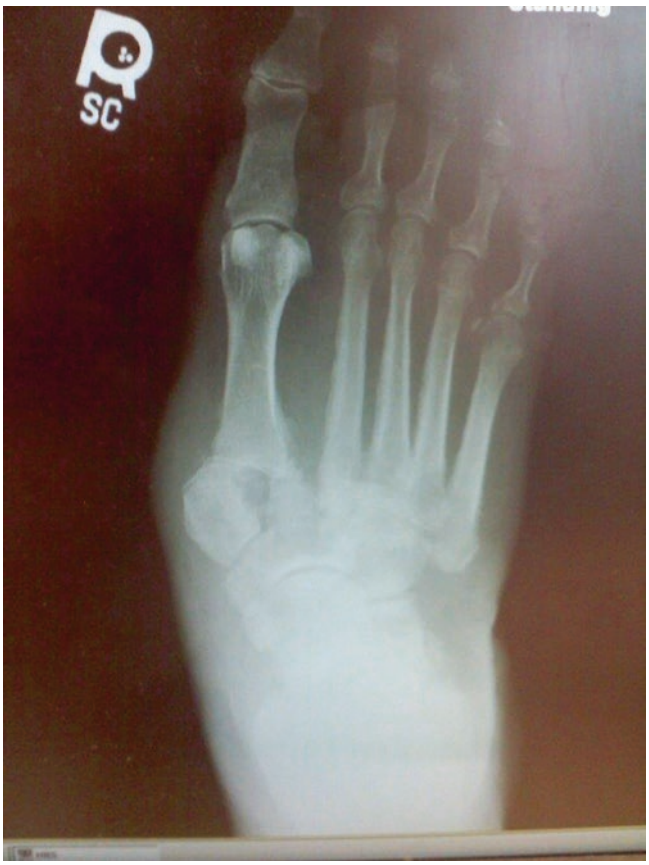

Fig. 62.7 Late development early coalescent Charcot arthropathy involving the Lisfranc and intercuneiform joints

be established. In cases of abscess formation, operative incision and drainage, and, rarely, amputation may be necessary.

The cornerstone of treatment for acute Charcot neuroarthropathy is protected offweighting with total contact casting. The patient must remain completely nonweightbearing on the affected limb using any manner that will guarantee patient adherence. This may be accomplished via crutches, roller cart, or wheelchair depending on patient psychosocial capabilities and available resources.

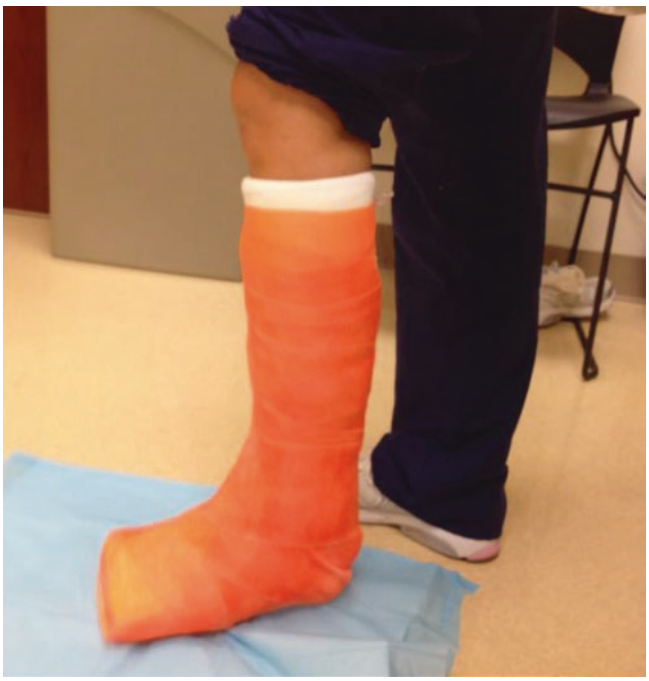

Fig. 62.8 Total contact cast for treatment of acute Charcot neuroarthropathy

Clinicians should be aware of the protracted time frame for the acute phase to transition into the coalescent phase where protected weightbearing is possible. Sinacore studied 30 subjects with 35 acute onset presentations of Charcot of the foot and ankle. The midfoot was most commonly involved (46 patients), followed by the hindfoot (23 patients), forefoot (20 patients), and ankle (11 patients). All patients were treated with total contact casting, and the healing endpoint was defined as discontinuation of the necessity for TCC as determined by the treating physician. In 100% of cases, the average healing time was 86 ± 45 days [43]. Providers may take from this a rule-of-thumb of 1 to 2 months for transitioning out of the acute Charcot phase.

Total contact casting (TCC) (Fig. 62.8) is a modified method of below the knee cast that involves applying minimal under-cast padding to the extremity and using a cast that conforms to the shape of the leg and foot. This device attempts to maintain the shape of the foot during the acute destructive process of Charcot. The patient should be maintained in the TCC until the acute phase of destruction has resolved with cast changes weekly at first until the initial edema resolves. The TCC requires considerable training to appropriately apply, and if placed incorrectly may result in abrasions, ulcerations, and an increased potential for limb amputation. This device should be applied only by trained specialists. Pinzur et al. found patients were able to safely bear weight in a TCC with biweekly changes lasting an average of 5.8 weeks. Patients were considered safe for transition into prescription shoes at an average of 12 weeks [44]. In the emergency department, an appropriate alternative is to apply a removable cast walker to the patient with instructions not to remove (Fig. 62.9).

Charcot arthropathy involving the ankle joint is somewhat different in outcomes compared with pedal joints and often involves a surgical approach. Schon et al. found an improved overall outcome of this disorder when treated surgically as opposed to nonsurgically with casting and bracing. They found a greater loss of correction with nonsurgical care and improved success rates with surgical intervention [45].

The effect of bisphosphonate therapy for the treatment of acute Charcot arthropathy has revealed conflicting and controversial results. Jude et al. in 2001 randomized 39 patients with acute Charcot to either a single intravenous dose of pamidronate 90 mg or placebo (saline) in a double blind manner. Patients were then followed for 12 months during which skin temperature, bone-specific alkaline phosphatase, and deoxypyridinoline crosslinks were measured. Patients given the pamidronate were observed to have an initial reduction in bone turnover as compared with placebo with similar levels at the end of the study [46]. This was the first study to examine a potentially definitive treatment for Charcot arthropathy. Subsequently, several studies examined the outcomes of bisphosphonate therapy on acute Charcot with one study finding increased time to clinical resolution with zoledronic acid and possibly extending the time to resolution [47].

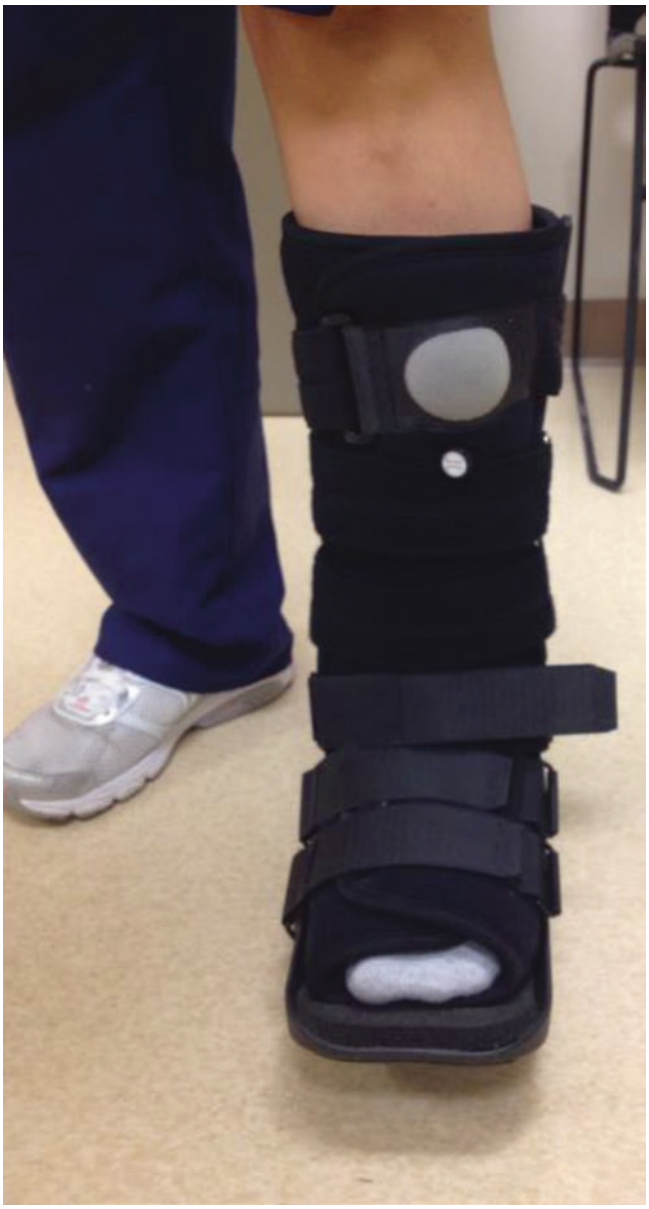

Fig. 62.9 Removable cast walker as an alternative to total contact casting

Significant methodological flaws in this body of research demonstrate low experimental numbers, various treatment methods (e.g., intravenous versus oral formulations and different experimental drugs), and lack of long-term follow-up [48, 49]. Two systematic reviews have stated that skin temperature and inflammatory markers decrease with bisphosphonate therapy, but studies have failed to demonstrate improved clinical outcomes and might even prolong the resolution phase [50, 51]. Due to the lack of long-term outcomes and questionable results, we currently recommend against the use of bisphosphonates for acute Charcot neuroarthropathy.

Currently, the joint destruction and subsequent deformity of Charcot are irreversible. Thus, long-term care consists of shoe gear modifications, sometimes requiring custom shoes, custom foot orthoses, and regular serial observation by a foot specialist. Some physicians prefer to place these patients into a Charcot Restraint Orthotic Walker (CROW), which is a custom molded below knee brace that attempts to redistribute plantar pressures (Fig. 62.10). The primary goal is prevention of ulceration and amputation.

In certain situations, surgical intervention may be necessary, including demonstrated instability, preulcerative callus formation, and ulceration. Surgical options are beyond the scope of this chapter but generally include tendoachilles lengthening to reduce forefoot pressures, ostectomy procedures to reduce bony prominence, realignment arthrodesis to create a more functionally stable and plantigrade foot, and limb amputation. Each of these reconstructive procedures should be considered salvage methods in an attempt to avoid amputation.

Outcomes for patients with Charcot arthropathy of the foot vary. When considering the risk of amputation, it is clear that patients with mild joint destruction and minimal to no subsequent deformity are at relatively low risk. Sohn et al. retrospectively reviewed a Veterans' Affairs national cohort of 911 patients with incident Charcot arthropathy and 15,117 patients with diabetic foot ulcers (without amputations). They found the overall amputation rate for patients with Charcot was not significantly different from the overall diabetic population with foot ulcers. However, patients with both Charcot and the

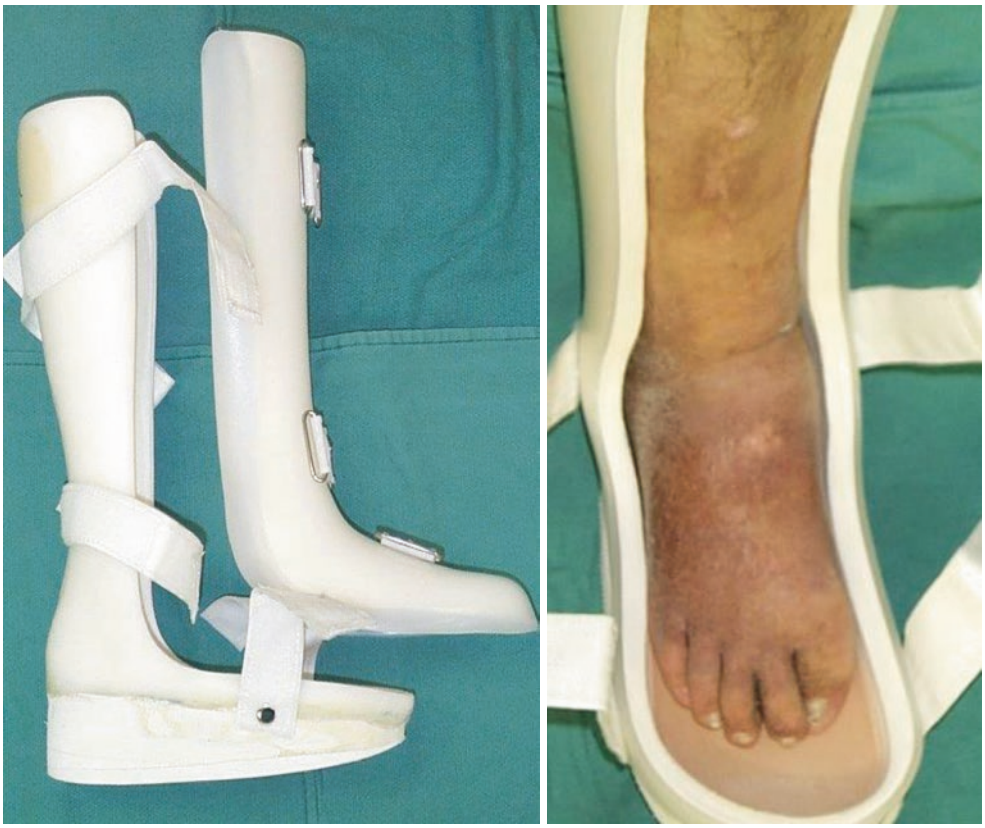

Fig. 62.10 Custom-made Charcot Restraint Orthotic Walker (CROW) for offweighting the Charcot foot

presence of a foot ulcer were 12 times more likely to undergo a limb amputation, and patients with ulcer alone were 7 times more likely to undergo a limb amputation than those with Charcot alone [9]. This demonstrates that Charcot alone does not increase the risk of amputation, but when coupled with a foot ulcer, the risks are much higher.

When considering mortality, the risk profile is different. Sohn et al. examined a cohort of 1050 patients with Charcot arthropathy and compared them to diabetic patients with foot ulcer and those with diabetes alone. During a 5-year follow-up, they found 18.8% of patients with diabetes alone died, 37.0% with foot ulcer died, and 28.3% of the Charcot patients died. These researchers found the presence of Charcot independently and significantly increased the mortality rate of these patients [52].

These findings show that Charcot arthropathy is a complex and serious disease with a high rate of complications and potential morbidity and mortality. Physicians should maintain a very high index of suspicion in any diabetic patient with an acute presentation of erythema, edema, warmth, and new onset pain, despite the presence or absence of ulceration. A low threshold for acute splinting or casting with strict nonweightbearing protocols is the best current treatment to prevent long-term deformity and complications. Further research will be necessary to better elucidate the etiology and treatment of Charcot arthropathy.

Foot Amputation

Amputation is often the final stage of a long process, and in the diabetic this may often be considered a failure of prior care. However, a modified view of this concept may be appropriate to better understand the role of amputations in the foot. As discussed in the introduction to this chapter, major limb amputation (transtibial and transfemoral levels) has significant associated morbidity and mortality in the diabetic population. This may be observed through several lenses. First, these patients already have significant comorbidities, including advanced cardiovascular disease, among others.

Additionally, major limb amputation leads to a greater energy expenditure during walking. Waters et al. performed a seminal study in 1976 in which they compared several gait parameters in patients with above knee, below knee, and Symes ankle disarticulation amputations to a control group of normal subjects. They found improved gait velocity, cadence, stride length, oxygen uptake, maximum aerobic activity, and heart rate in patients with the more distal amputations [53]. Similarly, Gailey et al. compared transtibial amputee oxygen consumption, heart rate, and self-selected walking speed with a non-amputee control group. They also found increased metabolic costs in the amputee group. However, when stratifying the ampu-

tee group by length of amputation, they found a significant improvement in these parameters with increased amputation stump length [54].

However, it has been shown that length of the residual limb also correlates with mortality. There are no studies that show amputation itself leads directly to increased mortality. This correlation is likely complex and may be hypothesized as a population with significant comorbidities, especially cardiovascular, with the additional physiologic stressor of the amputation (increased energy expenditure and decreased ambulatory capability) accelerating the rate of development of the already present comorbidities.

Several research studies although have demonstrated improved mortality when comparing partial foot amputations to major limb amputations [55–57]. Table 62.2 shows a synthesis of studies that compared mortality by level of amputation: digital, below knee, and above knee levels. As shown, the 1 and 5 year mortality trends are decreased in favor of those that involve only the forefoot as compared with the leg.

With this general trend toward improved outcomes with more distal amputations, it is important to strongly consider partial foot amputations as significant tools to help patients maintain an active life and potentially improved life expectancy.

It is the intention of this section to provide clinicians with general information about the options available for pedal amputations. Interested surgeons should refer to other textbooks for procedure specifics. A variety of pedal amputations exist, all of which spare the remaining portions of the foot with variable success, most of which prevent major limb amputation.

The choice of which amputation to perform is highly patient-specific and depends on therapy goals, reason for amputation (cellulitis, abscess, gas gangrene, osteomyelitis, malignancy, or gangrene secondary to peripheral arterial disease). A detailed work-up must be performed including obtaining an appropriate history, physical, and laboratory and imaging data. Additionally, the preoperative functional status and psychosocial history must be evaluated to appreciate the anticipated postoperative level of function.

Table 62.2 Mortality percentages by level of lower limb amputation demonstrating improvements with increasingly distal amputations [55–57]

Amputation level	30 day mortality %	1 year mortality %	5 year mortality %
Toe	1.7	6.6	46
TMA	2.7	8.5	45
BKA	7.0	25.5	56
AKA	11.1	49.4	70

Peripheral arterial disease is a major risk factor for failure of partial foot amputations [58]. Patients with peripheral arterial disease should undergo a comprehensive evaluation with noninvasive vascular testing, angiography, and consultation with a vascular surgeon. Revascularization should be performed before amputation unless an acute infection necessitates incision and drainage with debridement. It is sometimes necessary to stage the definitive amputation after emergent debridement and subsequent revascularization. Very little evidence is available to assist caregivers in determining the best timing of amputation after revascularization.

Caselli et al. attempted to answer this question by retrospectively reviewing 23 diabetic patients with ischemic foot ulcers who underwent successful transluminal percutaneous angioplasty (PTA) and 20 patients who underwent unsuccessful PTA. They used transcutaneous oxygen pressure measurement ($TcPO_2$) on the dorsal surface of the foot before and after PTA at 1, 7, 14, 21, and 28 days postoperative as a marker of improved perfusion. In the successful revascularization group, $TcPO_2$ measurements progressively improved and peaked at 4 weeks while the unsuccessful group saw no significant rise in $TcPO_2$. These researchers suggested waiting 3 to 4 weeks for the definitive amputation when delay is possible [59]. Currently, timing of amputation after revascularization is determined anecdotally based on clinician experience rather than via sound research-based evidence. Clearly, further research with well-designed prospective methodology is necessary.

Digital Amputation (Fig. 62.11)

Indications for digital amputation in the diabetic foot most commonly include isolated gangrene of a toe, osteomyelitis, and severe soft tissue infection. Amputation of a single digit may be performed along any portion of the length of the digit including the distal or proximal interphalangeal joint or at the metatarsophalangeal joint. When possible, it is preferable to leave as much of the digit as possible. The remaining stump acts as to prevent the contiguous digits from falling into the space previously occupied by the amputated digit. Hammertoe contractures though must be taken into consideration as this may cause the remaining post-amputation portion of the toe to be plantar flexed with increased distal pressures and future ulceration.

Ray Amputation

Amputation of a toe (Fig. 62.12) and part or all of the associated metatarsal is another common procedure that is

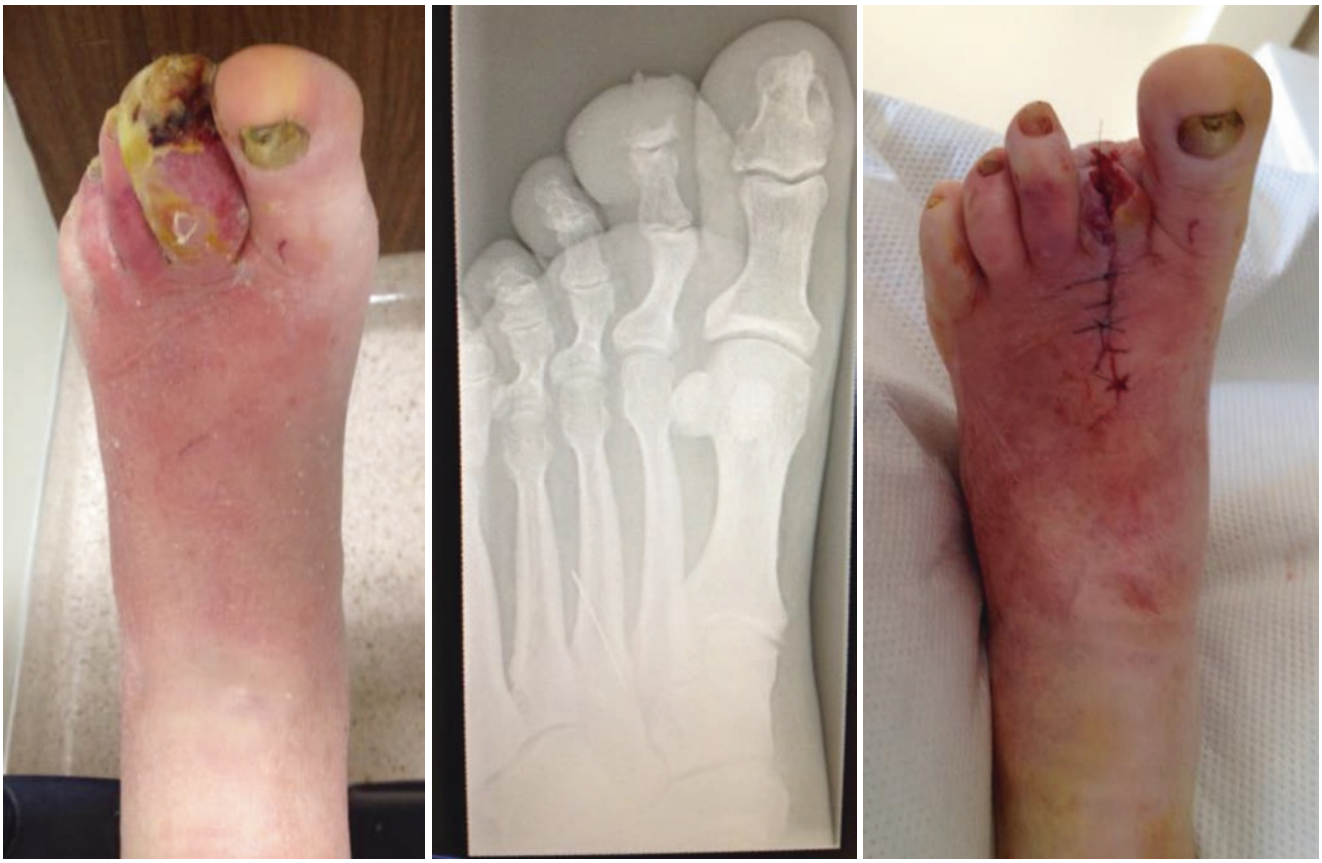

Fig. 62.11 Digital amputation with disarticulation at the metatarsophalangeal joint on patient with second toe distal phalangeal osteomyelitis and necrotizing abscess formation. Partial closure immediately with delayed primary closure 3 days later

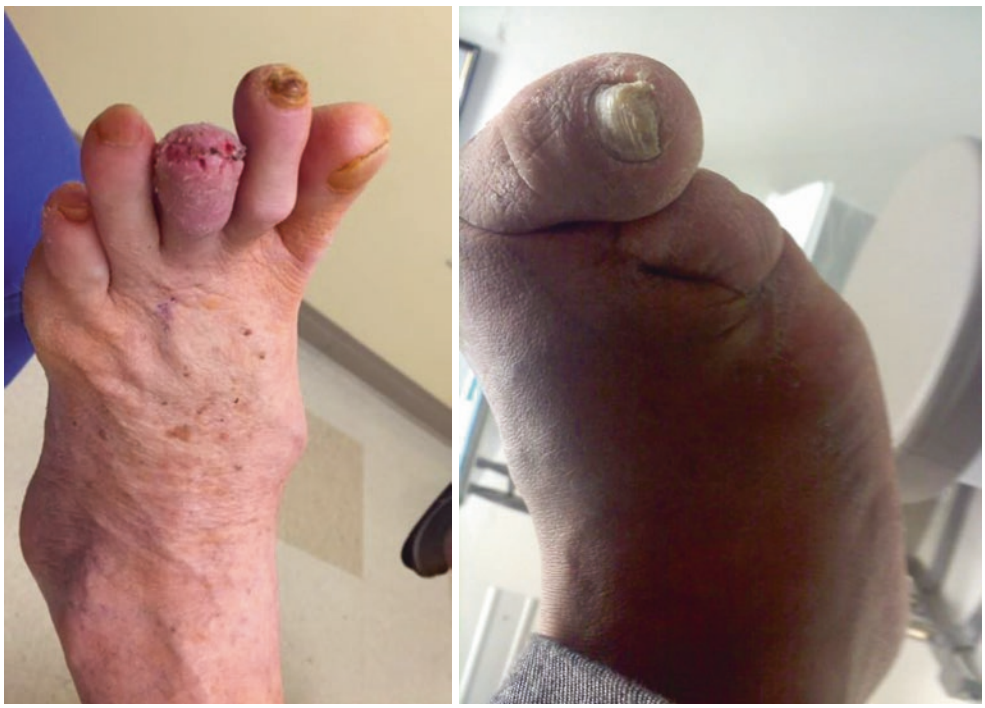

Fig. 62.12 Partial toe amputations. Left: 2 weeks postoperative with uneventful healing. Note buttressing effect the residual toe provides. Right: dislocation of first metatarsophalangeal joint with almost 90° hallux abduction due to prior lesser toe amputations and loss of lateral buttress

commonly performed on patients with osteomyelitis of a digit that extends into the metatarsophalangeal joint or abscess of the affected ray. Due to firm fascial septae that separate the individual rays, it is often possible to resect a ray in an isolated manner. This procedure is easily performed with a racket-type incision that extends proximally along the metatarsal to the necessary amputation level (Fig. 62.13).

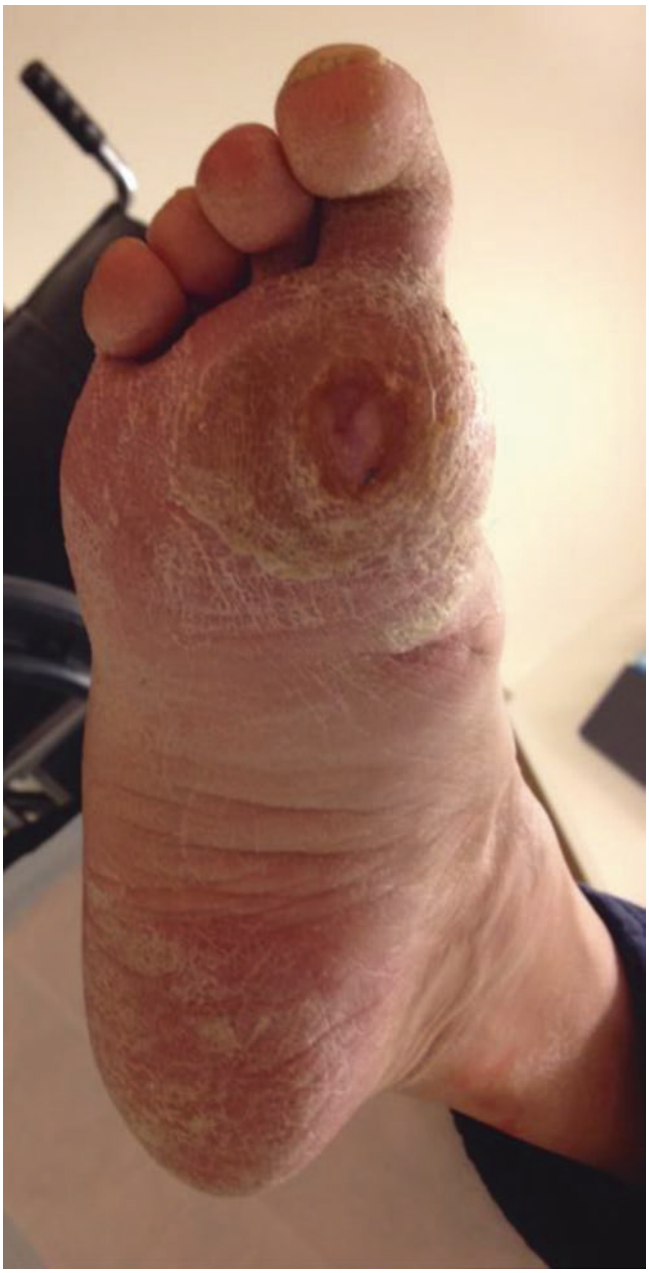

Fig. 62.13 Recurrent neuropathic ulcer status post partial first ray amputation. Note the lesser hammertoe contractures and ulceration secondary to transfer pressure

Transmetatarsal Amputation

Amputation of all toes and a portion of their associated metatarsals, the transmetatarsal amputation, is a powerful and highly useful procedure in the diabetic foot. This procedure is indicated in forefoot gangrene, osteomyelitis, abscess, or forefoot tumor (Figs. 62.14 and 62.15). Due to increased plantar pressures and altered gait kinematics [60] percutaneous Achilles tendon lengthening is commonly performed with this procedure to prevent postoperative plantar stump ulceration. This procedure has a high success rate, allowing patients to ambulate with minimal shoe modifications.

Isolated and Panmetatarsal Head Resection

Although not considered true amputations, removal of an isolated metatarsal head or removal of all of the metatarsal heads (panmetatarsal head resection) may be important alternative tissue-sparing procedures useful in specific situations. These include neuropathic plantar ulcers and isolated or multiple metatarsal head osteomyelitis without extended bone or soft tissue involvement. A retrospective review of 34 panmetatarsal head resection procedures with average follow-up of 20.9 months revealed an overall success rate of 97% with 1 ulcer recurrence and no amputations [61].

Figure 62.16 demonstrates the utility of this procedure. Patient SR was a 48-year-old long-term diabetic male with a chronic right foot plantar neuropathic ulcer that did not respond to several offweighting modalities. The patient had previously undergone second and third metatarsal head resections with resultant rigid deformity. Due to peripheral arterial disease, the patient underwent a femoral to posterior tibial bypass and 1 month later panmetatarsal head resection. At 5-year follow-up, the patient remained ulcer free. Internally, offweighting the forefoot successfully resolved this patient's ulcer.

Tarsometatarsal (Lisfranc) Midtarsal (Chopart) Amputations (Figs. 62.17 and 62.18)

These more proximal foot amputations have historically been less utilized due to increased long-term complications, especially plantar reulceration [62]. Previously, this was due to a less biomechanically stable foot with focal plantar pressures and the absence of adequate prosthetic devices. When possible, a more distal amputation such as the transmetatarsal level is preferable. However, in cases of more significant tissue loss where limb

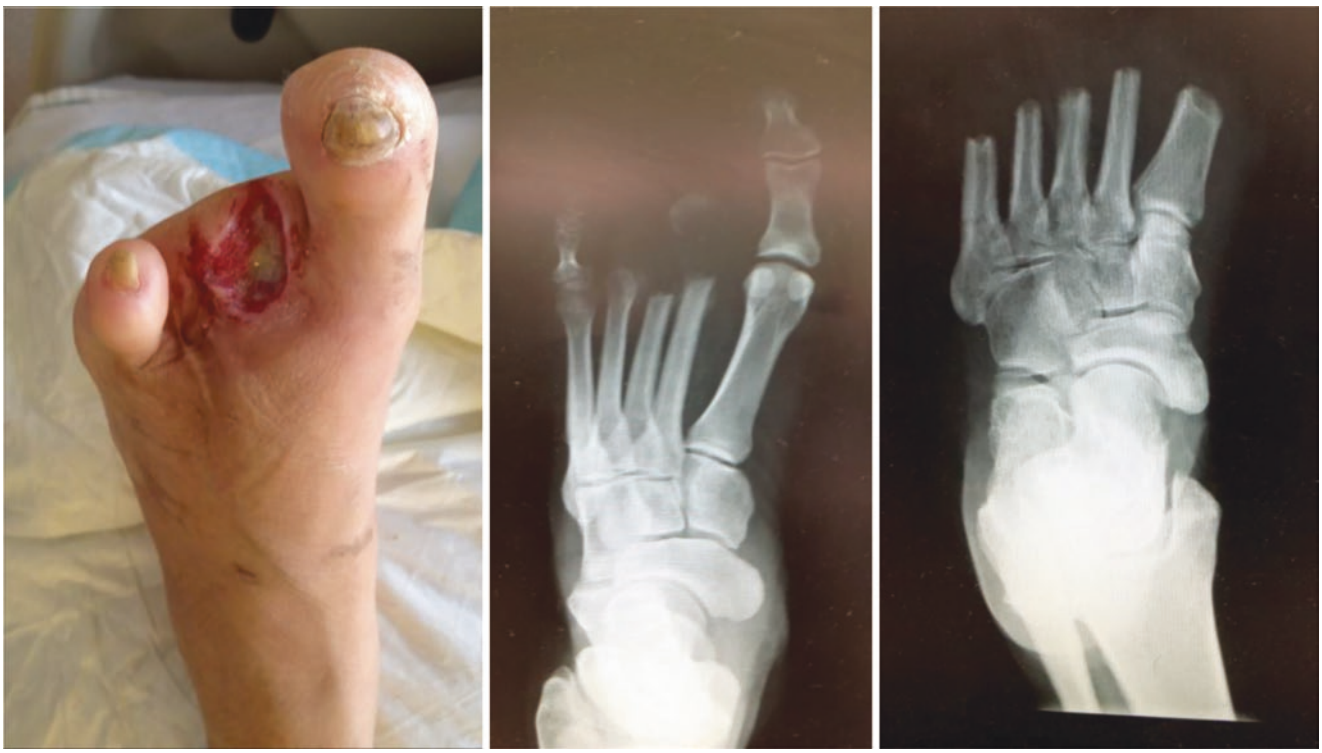

Fig. 62.14 Series of a patient who underwent transmetatarsal amputation after multiple prior digital and partial ray amputations with osteomyelitis of the second metatarsal head and a nonfunctional forefoot. Left: preoperative clinical appearance with visible second metatarsal head. Middle: preoperative dorsoplantar radiograph with second metatarsal head fracture and osteomyelitis. Right: postoperative dorsoplantar radiograph after successful transmetatarsal amputation

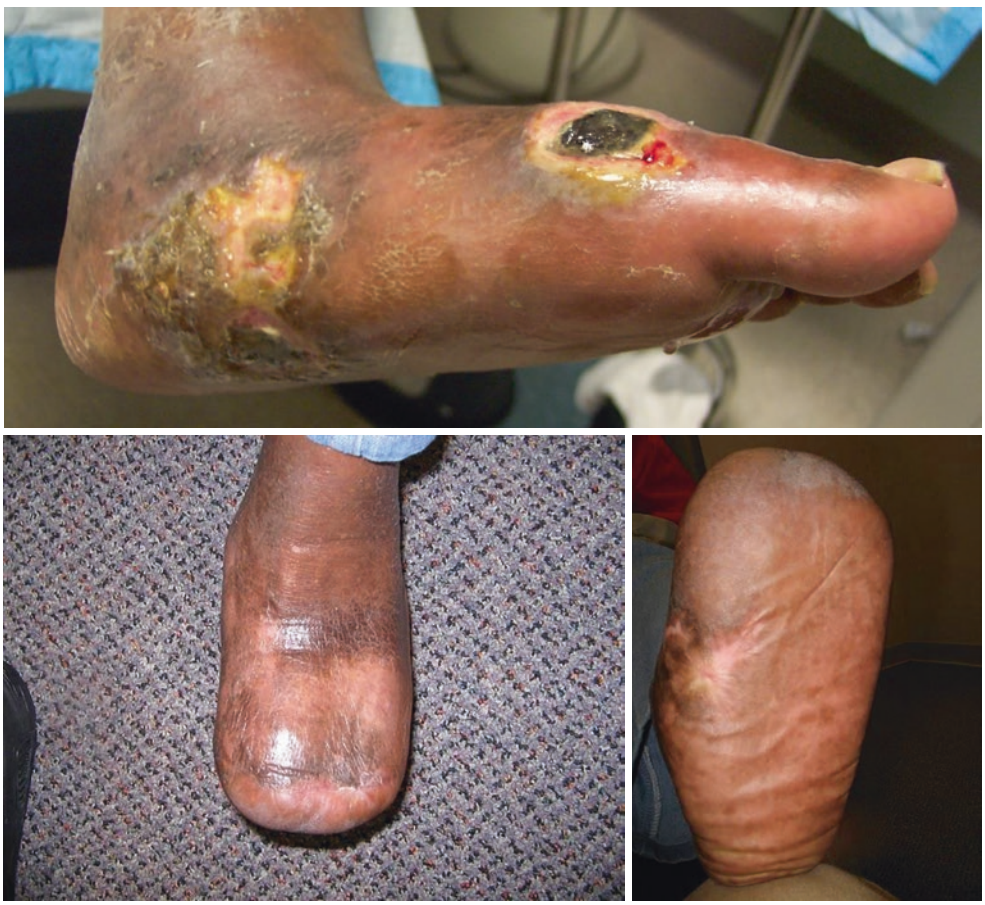

Fig. 62.15 Diabetic male with severe peripheral arterial disease and critical limb ischemia (top image). Patient underwent endovascular intervention and staged transmetatarsal amputation with Achilles tendon lengthening. Dorsal weightbearing view (bottom left) with plantar view (bottom right) demonstrating successful healing without recurrent ulceration

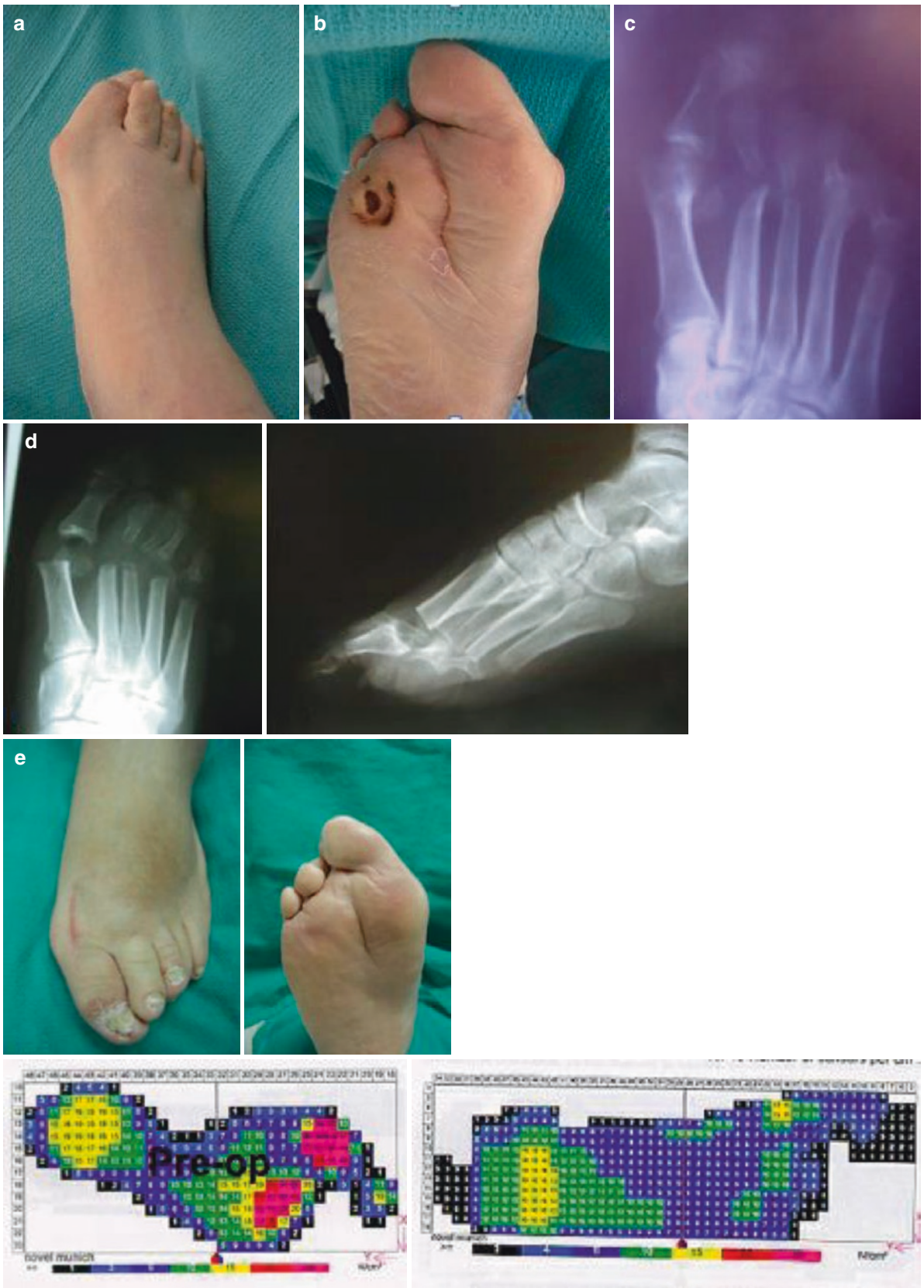

Fig. 62.16 Clinical and radiographic image series of patient SR who underwent panmetatarsal head resection after revascularization for non-healing plantar neuropathic ulceration. Images **A, B, C** = preoperative clinical and radiographic appearance. **D** = Postoperative radiographic appearance. **E** = 5-year follow-up clinical appearance. Note ulcer-free appearance. Bottom row shows E-med pressure sensing system with preoperative (left) and postoperative (right) pressures (red = highest pressures, black = lowest). Note the significant long-term pressure reductions

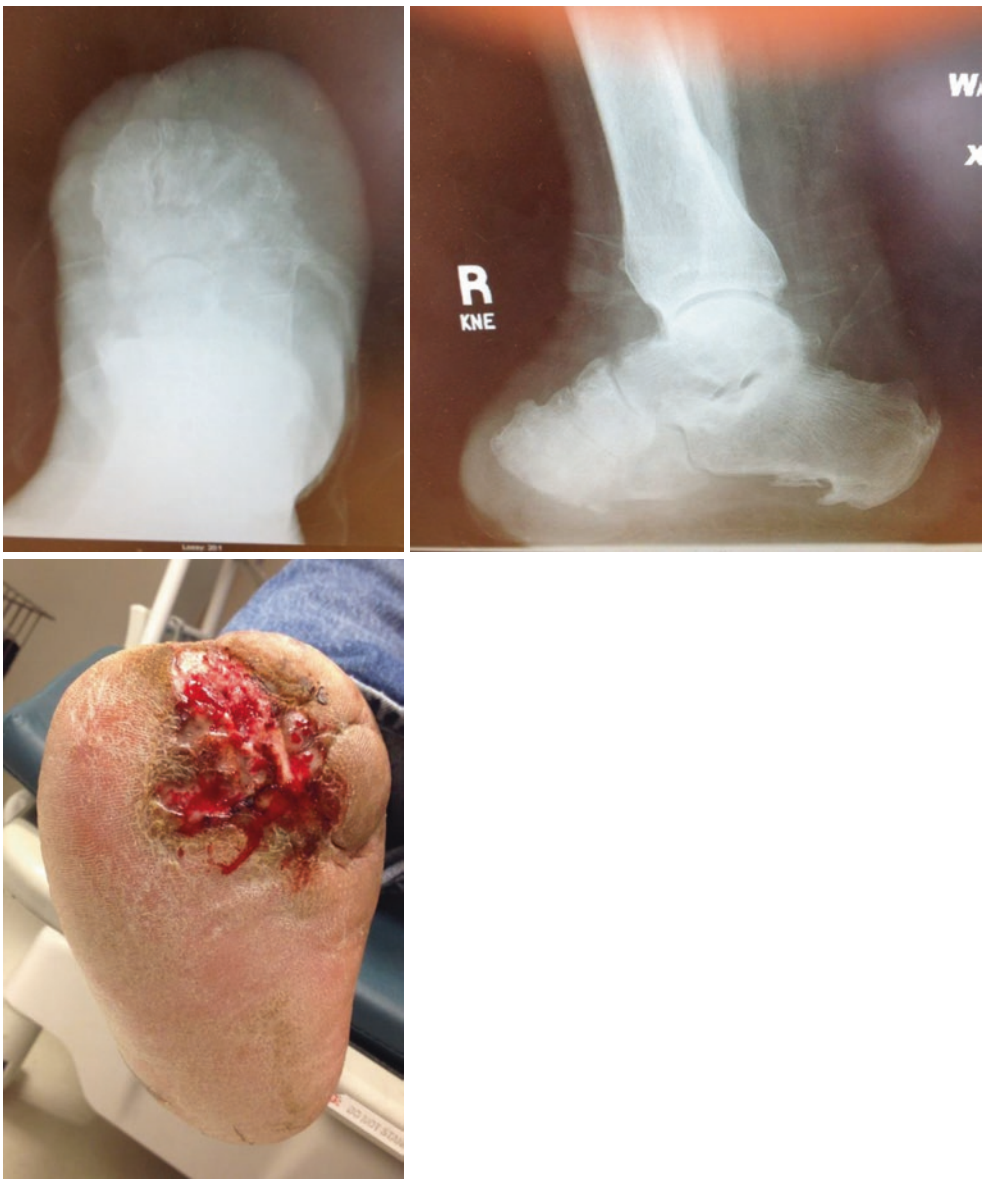

Fig. 62.17 Right foot Lisfranc amputation with removal of fifth metatarsal base and peroneus brevis attachment. Altered biomechanics led to varus foot position with lateral overload and recurrent plantar ulceration

salvage is attempted, these procedures have an important role. Preservation of the bases of the first and fifth metatarsals when possible retains their respective tendon insertions with improved outcomes. Accessary soft tissue balancing techniques improve the mechanical function of the residual foot. These include gastrocnemius recession, Achilles tendon lengthening, Achilles tenotomy or tenectomy, tibialis anterior transfer, peroneus brevis transfer, and posterior tibial tenotomy [62, 63].

The partial foot amputations outlined above have variable outcomes. The majority of clinical studies are retrospective in nature, and further well-designed prospective comparative studies are necessary. Given this limitation, there is a relative consensus that isolated partial or total digital amputations generally have positive results. However, amputation of the hallux or first ray is a unique situation that may have variably poor outcomes. In 1997, Murdoch et al. retrospectively reported on a 10-year cohort of diabetic patients who underwent either great toe or partial first ray amputations. Sixty percent of these patients eventually underwent a second amputation, 17% underwent a later below knee amputation, and 11% had a transmetatarsal amputation on the same extremity. The mean time to second amputation was 10 months from the index procedure [64]. Kadukammakal et al. retrospectively reviewed 48 patients who underwent 50 partial first-ray amputations between 2003 and 2009 and found 24 cases required further surgical intervention with 12 of those converted to a transmetatarsal amputation with a mean time of 9 months to definitive amputation [65]().

Similarly, Izumi et al. in 2006 retrospectively analyzed a population of 277 diabetic patients who underwent a first-time amputation. They looked at repeat amputation after first amputation at 1, 3, and 5 years [66]. They found the reampu-

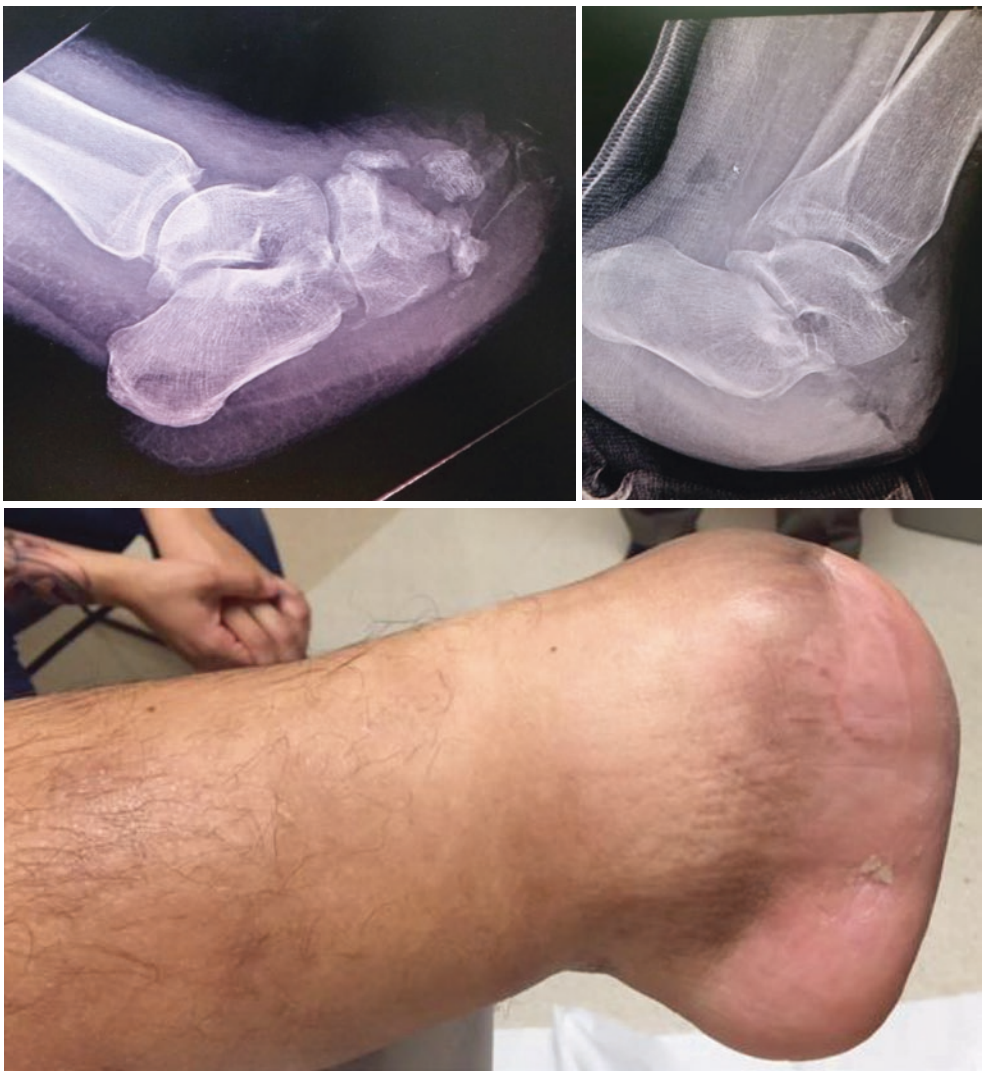

Fig. 62.18 Chopart amputation for lesser tarsal osteomyelitis after failed Lisfranc amputation. Preoperative radiograph (left). Postoperative radiograph (right) and clinical appearance (bottom) after successful Chopart amputation and Achilles tendon lengthening

Table 62.3 Ipsilateral limb amputation rates by level of original amputation level [67]

Level of index amputation	1-year (%)	3-years (%)	5-years (%)
Toe	22.8	39.6	52.3
Ray	28.7	41.2	50
Transmetatarsal	18.8	33.3	42.9
Major limb	4.7	11.8	13.3

tation rates noted in Table 62.3. As indicated in the table these researchers found an increasing trend in future amputations over time. However, the rate of change decreased when comparing toe and ray amputations to the transmetatarsal level, indicating the inherent problematic long-term success of the more minor pedal amputations. This increased complication rate is due to the altered biomechanics of the residual foot in otherwise ambulatory patients. For example, after partial first ray amputation, it is highly predictable to see hammertoe contractures of the remaining toes and altered weightbearing plantar pressures. These deformities then predispose the neuropathic patient to further ulceration, infection, and subsequent amputation.

The transmetatarsal amputation has gained popularity as an increasingly successful forefoot amputation. The aforementioned studies demonstrate the decreased reamputation rates versus hallux and partial first ray amputation. This was shown early in a retrospective cohort study of 53 patients undergoing first-time amputation with a success rate of 37.1% in patients undergoing partial first ray amputations and 93.3% in patients undergoing transmetatarsal amputation [67]().

Conclusion

All interventions discussed herein rely fully on involvement of the patient and adherence to treatment regimens. Unfortunately, this may be difficult in practice. Nonadherence in patients with diabetic foot complications is high.

Depression has a significant effect on the diabetic patient and has been shown to decrease health-related quality of life, decrease self footcare, and increase number and severity of diabetes-related complications [68, 69]. Major depression has been linked with a two-fold increased risk of incident ulcers [70] and a five-fold increased risk of ulcer recurrence [71]. Depression also increases the amputation risk with a 33% increased risk of major amputation and 12% increased risk of any amputation (major or minor) [72].

Specialists caring for patients with diabetic foot complications must be cognizant of the home and social environment as well as any individual factors that may involuntarily increase nonadherence to medical therapy. Time should be taken to educate the patient about his or her situation and the steps necessary for care, and it must be determined if the patient is cognitively able to understand the various needs to effect positive outcomes.

The complications associated with the diabetic foot are highly significant and require greater focus to improve patient outcomes. Due to the complexity of the diabetic patient, no single medical provider can successfully perform all of the necessary interventions. Thus, a team approach is integral to appropriate care. The team approach, in which all providers involved with limb preservation participate in the joint care of patients, has become increasingly common with designated amputation prevention centers to focus on all aspects of the diabetic foot. Table 62.4 lists the possible members of the amputation prevention service [73], but it must be understood that at the center of this team is the patient.

Several recent studies have demonstrated both improved outcomes and decreased healthcare costs with this team approach. VanGils et al. reported on the outcomes of a collaborative approach between podiatry and vascular surgery services in a Veterans' Affairs population. During a 55-month follow-up, they found an 86.5% limb loss avoidance rate at 3 years which remained 83% at 5 years [74]. Similarly, a collaborative approach including vascular surgery, orthopedics, endocrinology, plastic surgery, and nursing in a Turkish limb preservation service found an overall amputation rate of 39.4% with 30% below knee amputations [75], an improvement in the rate of major amputations. Driver et al. reporting on the outcomes of a multispecialty limb preservation service, found an 82% decrease in any lower limb amputations over a 4-year period despite a rising number of diabetic patients [76].

Table 62.4 Potential members of an amputation prevention service

Certified diabetes educator
Endocrinologist
General surgeon
Infectious disease specialist
Internist
Nephrologist
Nurse
Nutritionist
Podiatrist/orthopedist
Pedorthotist/orthotist/prosthetist
Psychologist/psychiatrist
Vascular surgeon

In conclusion, diabetic foot complications were a previously poorly understood phenomenon that today has demonstrated significant improvements in outcomes. When understood properly and treated with a comprehensive interprofessional care model diabetic foot ulcers, Charcot neuroarthropathy, and infections such as osteomyelitis may be successfully treated with improved patient ambulatory activity and quality of life.

Multiple Choice Questions

1. Five year mortality rate for patients with neuropathic foot ulcers:
   (a) 30%
   (b) 35%
   (c) 40%
   (d) **45%**
   (e) 50%
2. Diabetic foot ulcers:
   (a) Are not preventable
   (b) Are mostly not preventable
   (c) **Are mostly preventable**
   (d) Are unavoidable
   (e) None of the above
3. Compared with some types of cancer, 5-year mortality rates from neuropathic ulcers and amputations:
   (a) **Are higher**
   (b) Are lower
   (c) Are equal
   (d) Have not been compared
   (e) Are not comparable
4. A crucial initial event on the development of diabetic foot ulcers:
   (a) Low grade microtrauma
   (b) **Loss of protective sensation**
   (c) Lower limb ischemia
   (d) Infection
   (e) Structural deformities
5. The stage at which the typical foot ulcer healing process stalls:
   (a) The hemostatic inflammatory phase
   (b) **The proliferative phase**
   (c) The remodeling phase
6. Compared to patients without diabetes, the risk of amputation in patients with diabetes and peripheral artery disease is:
   (a) Two times higher
   (b) Three times higher

(c) Four times higher
(d) **Five times higher**
(e) Six times higher

7. Historical components of the vascular risk spectrum include:
   (a) Macrovascular disease
   (b) Microvascular disease
   (c) Functional microvascular disease
   (d) A and B are correct
   (e) **A, B, and C are correct**
8. According to the UKPDS trial, each 1% increase in glycosylated hemoglobin increases the risk of peripheral artery disease:
   (a) 12%
   (b) **28%**
   (c) 34%
   (d) 43%
   (e) 51%
9. Independent risk factors for peripheral artery disease include all of the following, except:
   (a) Hyperglycemia
   (b) Smoking
   (c) Systolic blood pressure
   (d) **Diastolic blood pressure**
   (e) Dyslipidemia
10. Different studies have shown that a team approach reduces the risk of lower limb amputations approximately:
   (a) 30%
   (b) 40%
   (c) 50%
   (d) **80%**
   (e) Compared to traditional management, no reduction have been demonstrated.

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Diabetes and Cancer

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Chapter Objectives

- The prevalence of diabetes mellitus type 2 and cancers of various sites is dramatically increasing nowadays. It was established that diabetes mellitus (mainly type 2 diabetes mellitus) predisposes do oncogenesis in various human organs.
- The main factors leading to neoplastic transformation in diabetics are hyperinsulinaemia, hyperglycaemia and chronic inflammation induced by excessive adipose tissue.
- Anti-diabetic medications interfere with the risk of neoplastic transformation—some of them elevate the risk, some reduce the risk and some express inconsistent activity.
- Certain anti-diabetic medications express potential usefulness in improving effectiveness of conventional chemotherapy.
- Diabetics with T2DM and coexisting neoplasm have worse disease-free and overall survival than patients with neoplasm but without T2DM.

Introduction

Diabetes mellitus (DM), one of the most common diseases all around the world, comprises a large group of metabolic disorders. DM is characterized by persistent hyperglycaemia caused by inaccurate function of insulin or its reduced excretion from pancreatic beta cells. Long-lasting hyperglycaemia results in damage and improper function of various organs. The morbidity of T2DM is rapidly increasing especially in middle-aged people (45–65 years). Interestingly, recent evidence implies that there is a significant correlation between DM and neoplastic transformation [1–9]. The association was observed both for type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) [10]; nevertheless the majority of studies concern T2DM [11, 12]. It has been shown that DM (especially T2DM) increases the risk of various cancers in men and women [10, 11]. Up to now, little is known about the links between T1DM and carcinogenesis. Nevertheless, it was observed that T1DM enhances the overall risk of pancreas, liver, oesophagus, colon and rectum, and stomach, thyroid, brain, lung, endometrium, ovary, cervix, squamous cell skin cancers and acute lymphatic leukaemia in women [10–13]. The strongest association between DM and carcinogenesis is observed for pancreatic and liver cancers in patients with T2DM [14]. Additionally, according to the current knowledge there is also a relationship between neoplastic transformation and anti-diabetic medications [6]. However, the exact mechanisms leading to this connection need further investigation [1, 15].

Historical Facts

The first description of diabetes (a state of polyuria) was found in the Ebers Papyrus in 1552 BC by Egyptian physician Hesy-Ra. This description was found in Thebes (Egypt) in 1862 AD by Egyptologist Georg Ebers. The term “diabetes” comes from Greek meaning “siphone” and was intro-

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duced by Areteus from Cappadocia (81-138 AD) who described main symptoms of this disease [16, 17]. The main differences between the two most common types of DM (type 1 and type 2) were observed and described by Himsworth in 1936 [18].

Epidemiology

The number of persons with diabetes mellitus in 2021 estimated by the International Diabetes Federation (IDF) among adults (aged 20–79 years) reached 537 million of people [19]. Nevertheless, approximately 50% of DM cases remain undiagnosed. The IDF estimates that in 2040 the number of persons with diabetes will amount 785 million people [19].

The World Health Organization (WHO) has declared that cancer is the leading cause of death worldwide, accounting for nearly ten million deaths in 2020 [20]. The most common new causes of cancer in 2020 were breast (2.26 million cases), lung (2.21 million cases), colon and rectum (1.93 million cases), prostate (1.41 million cases), skin (non-melanoma) (1.20 million cases) and stomach (1.09 million cases) [20]. The most common causes of cancer death in 2020 were lung, colon and rectum, liver, stomach and breast, and according to the WHO, the annual incidence of new cancer cases will reach 22 million in the next two decades [20]. Normal cells transform into malignant cancer cells through a complex process, including initiation, promotion and progression involving more aggressive growth, angiogenesis and metastases [21].

Types of Diabetes Mellitus

Diabetes is a group of disease entities that can be classified as follows:

T1DM (previously known as "insulin-dependent diabetes mellitus") is caused by autoimmune or idiopathic process of self-aggression leading to rapid destruction of pancreatic β-cells. As a result, the level of insulin, the pancreatic hormone responsible for maintaining glycaemic control, is minimal or undetectable. T1DM usually appears as ketoacidosis with its main symptoms including polyuria, polydipsia, nausea, vomiting, stomachache, weakness, acetone breath and Kussmaul breathing. T1DM concerns 5–10% of all cases of diabetes. The autoimmune process is characterized by the presence of four types of antibodies: ICA (islet cell antibodies), IAA (insulin autoantibodies), anti-GAD (anti-glutamid acid decarboxylase), IA-2 and IA-2B (tyrosine phosphatase-related islet antibodies). These antibodies can be detected months of even years before first symptoms of the disease. Generally, T1DM is not an inherited disease; however, there is a proven genetic predisposition determined by HLA (human leukocyte antigens). The highest susceptibility to T1DM occurs in patients with haplotype HLA-DRB1*03 (DR3) or HLA-DRB1*04 (DR4) with DQB1*03:02 (DQ8) [22]. Conversely, the HLA-DQ6 haplotype is considered to protect against developing T1DM. T1DM may appear at any age but is usually diagnosed during childhood (before 30 years). The exception is LADA (Latent Autoimmune Diabetes of Adults) that occurs in adults. T1DM treatment is based on multiple doses of exogenous insulin preparations for the lifetime.

T2DM (previously known as "non-insulin-dependent diabetes mellitus") is the most common form of diabetes (up to 95% of all cases). T2DM is generally characterized by insulin resistance of insulin-dependent tissues (adipose tissue, liver and muscle cells) leading to improper, excessive secretion of insulin and hyperinsulinaemia [23]. Insulin insensitivity causes a decreased glucose uptake of target tissues and increased serum glucose level [18]. Other pathologies in T2DM comprise increased amount of circulating inflammatory cytokines, adipokines, lipotoxic free fatty acids or amyloid deposits in pancreatic islet cells [24]. Risk factors of T2DM include genetic, inherited predisposition, sedentary lifestyle, obesity, ageing, cigarettes smoking and/or excessive alcohol consumption. This type of diabetes commonly affects middle-aged or older people albeit during the last two decades an increasing trend has occurred in adolescents. The genetic susceptibility to T2DM is more significant than observed in T1DM. Confirmed positive family history is associated with a 2–4 times increased risk of T2DM [24]. Recently discovered genes connected with high risk of developing T2DM are insulin receptor, potassium channels, proteases or transcription factors genes [16, 24]. The onset and early stages of T2DM are usually asymptomatic and progressive, and the slow development of the disease leads to delayed diagnosis. Being asymptomatic years before diagnosis, patients with T2DM are more prone to develop macrovascular or microvascular complications [24]. Management in T2DM is based on lifestyle changes, medical nutrition therapy, physical activity, diabetes education and support, and anti-diabetics [25–27]. Reducing body weight and physical activity are the firsts steps of therapy and essential in every stage of the disease. Pharmacotherapy must be patient-adjusted and includes a variety of glucose-lowering drugs such as biguanides (metformin), sulfonylureas, meglitinides, α-glucosidase inhibitors, thiazolidinediones (TZD), dipeptidyl peptidase four inhibitors (DPP-4-i), glucagon-like peptide-1 agonists (GLP-1) and sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors). If all mentioned methods are insufficient to achieve glycaemic control, insulin injections are required. Insulin may be used as monotherapy or in combination with other anti-diabetic drugs.

Additional etiological classes of diabetes include monogenic types, including MODY (maturity onset diabetes of the young), an inherited form caused by an autosomal dominant

gene. The pathophysiology of this type of diabetes is based on improper beta cells secretion of insulin with preserved insulin function [23]. Monogenic-type diabetes usually manifests in childhood (younger than 25) and is characterized by hyperglycaemia, insulin deficiency and mild clinical symptoms. Insulin resistance is not observed in MODY. Therapy in this type is of diabetes based on medical nutrition and oral anti-diabetics. Secondary causes of known aetiology include genetic defects of beta cells and insulin function, diabetes caused by drugs or other chemicals, infections, endocrinopathies, diseases of the exocrine pancreas or genetic syndromes.

Gestational diabetes (GDM) is a state of glucose intolerance that begins or is diagnosed during pregnancy. GDM is caused by insulin resistance during gestation and affects up to 7% of pregnant women. Insulin resistance in women with GDM is higher than in healthy ones, probably because of chronic insulin resistance observed in the first group [28]. During pregnancy, levels of hormones opposing insulin action (placental lactogen, oestrogen, progesterone and prolactin) are elevated, leading to excessive insulin secretion. Risk factors of GDM include obesity, GDM in previous pregnancies, positive family history of diabetes, current glucosuria and history of macrosomia in previous pregnancies. The management in GDM is based on medical nutrition, exercise and if this management is insufficient, insulin injections. Gestational diabetes is a risk factor for T2DM after childbirth T2DM [29]. Most of the studies about the association of diabetes are focused on Type 2 diabetes and cancer are focused on probably because of a higher prevalence of T2DM than T1DM.

Diabetes Mellitus and Oncogenesis—The Main Correlation

The association between DM and carcinogenesis was described for the first time in 1910 by Maynard and Pearson [30–31]. One hundred years afterwards, a consensus report presented by the American Diabetes Association (ADA) and the American Cancer Society (ACS) in 2010 described possible factors linking diabetes and cancer which could be divided into three main groups including modifiable risk factors, non-modifiable risk factors and biological links between DM and cancer [1, 32].

Links between DM and oncogenesis according to the ADA and the ACS:

- Modifiable risk factors:
  - overweight (BMI >25 and <30) and obesity (BMI >30)
  - physical activity (at least 5 days a week for 30 min a day reduces the probability of T2DM development)
  - smoking
  - alcohol abuse
- Non-modifiable risk factors:
  - sex (men are more prone than women)
  - age (adults aged between 55 and 60 years and older are more prone)
  - race (African Americans are more prone than Caucasians)
- Biological links:
  - hyperinsulinaemia (the effect of resistance to endogenous insulin or by exogenous insulin used as a medication).
  - hyperglycaemia
  - fat-induced chronic inflammation

Biological Linking Factors

(hyperinsulinaemia, hyperglycaemia, fat-induced chronic inflammation)

Role of Hyperinsulinaemia in Cancer Biology

Epidemiological studies have shown that high levels of insulin or C-peptide predict an increased risk for colorectal, breast, pancreas, bladder and endometrial cancer [21]. Insulin resistance and hyperinsulinaemia are important factors in the development of type 2 diabetes and additionally, insulin stimulates cell proliferation and promotes carcinogenesis in experimental animals [33]. Insulin resistance blocks signalling in the metabolic pathway involved in glucose metabolism, but does not inhibit activation of the cell signalling pathway involving cell differentiation [21]. The pro-neoplastic features of insulin are induced by activation of its receptors, Insulin Receptor [IR] and Insulin-like Growth Factor-1 is a polypeptide synthesized by almost all cells, although primarily by the liver [21]. Insulin resistance is able to activate the IGF-R receptor (IGF-R) because of approximately 60% structural homology of IGF-R and IR [33]. Similarly, IR may be stimulated by insulin and by both Insulin-like growth factors, IGF-1 and IGF-2 [34]. Ligand-induced IR autophosphorylation triggers intracellular mechanisms. The most important is activation of PI3K/Akt/mTOR (phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin) signalling pathway. Stimulation of PI3K/Akt/mTOR signalling pathway plays a critical role in oncogenesis [35]. Interestingly, activation of IGF-R (by both insulin and IGF) results in more significant pro-neoplastic effects than activation of IR. IR and IGF-R are critical in tumourigenesis also because of the fact that their concentration in various cancer cells is higher than in normal cells; thus the effect of insulin and IGF on neoplastic cells is enhanced [36, 37].

Indirect Effects of Hyperinsulinaemia on Cancer Biology

- Up-regulation of bioavailable IGF-1 by hyperinsulinaemia-induced down-regulation of IGF-binding protein 1,2 and IGF-binding protein-3. IGF-binding proteins are crucial in IGF serum transfer and activity. IGF binding to specific proteins does not exert its biological effects (biological inactivity) [36, 38].
- Up-regulation of IGF-1 in growth hormone (GH)-dependent manner (*Explanation:* Insulin stimulates growth hormone receptors (GHR) located in the liver leading to elevated release of GH. Subsequently, GH promotes IGF-1 synthesis) [39].
- Up-regulation of leptin, a pro-neoplastic adipokine [40].
- Reduced synthesis of sex hormone binding protein (SHBG) in the liver (*Explanation:* SHBG plays an important role in transfer and activity of sex hormones (testosterone, oestrogen). Reduced amount of SHBG leads to high bioavailability of sex hormones that presumably results in development of hormone-related cancers (e.g. endometrial, breast cancer) [41].

The Role of Hyperglycaemia in Cancer Biology

It was established that cancer cells require high glucose levels to grow and survive. Cancer cells are more sensitive to high serum glucose levels than normal cells because of their elevated concentration of glucose receptors (GLUT-1, GLUT-3). These cells are characterized by rapid development and metabolism, and therefore they require high glucose resources [42]. The link between glucose and cancer dates back to the Warburg effect, described by Otto Warburg in 1924, which states that "the prime cause of cancer is the replacement of the respiration of oxygen (oxidation of glucose) in normal body cells by fermentation of sugar [43]. Hyperglycaemia enables neoplastic transformation via stimulation of cells' quick growth and development, suppression of apoptosis and metastasis promotion [44]. Increased blood glucose levels affect the normal cellular system at three steps contributing to dysregulated growth: (1) DNA (genetic), (2) RNA transcription, (3) Protein (translation) [45].

Mechanisms Leading to Proliferative Activity of Hyperglycaemia [21, 44, 45]

- Elevated expression of PPAR α and γ (*peroxisome proliferator-activated receptor) (Explanation:* PPAR α and γ interfere with lipid metabolic pathways and speed up neoplastic cells development).
- *Elevated expression of* glucose receptors (GLUT-1, GLUT-3) leading to increased cellular glucose intake.
- Elevated expression of EFG (epithelial growth factor) that activates neoplastic pathways via binding to its receptor EGFR (epithelial growth factor receptor).
- Increased amounts of ROS (reactive oxygen species) and SOD (superoxide dismutase) leading to free radicals and other reactive molecules which could produce oxidative damage to DNA, mutations in oncogenes and tumour suppressor genes (*Explanation:* Oxidative stress is a critical triggering factor of insulin resistance, a tumour-promoting factor. In addition, it induces glucose-mediated inflammation and increased synthesis of transcriptional factors including NF-κB, activating protein-1 and early growth response-1. These mechanisms lead to tumour growth and metastasis).

Mechanisms Leading to Anti-apoptotic Activity of Hyperglycaemia [44]

- Reduced amount of PDH (prolyl hydroxylase) resulting in increased levels of HIF-α (hypoxia-inducible factor α) (*Explanation*: The majority of energy in tumour cells is produced in a hypoxic environment, via aerobic glycolysis. HIF-α is a critical factor involved in cancer cell existence in hypoxic milieu; thus hyperglycaemia-induced high amount of HIF-α promotes tumour cells growth and survival).

Mechanisms Leading to Hyperglycaemia-Mediated Metastasis [44–47]

- Increased zinc intake resulting in cancer cells dislocation (*Explanation:* Increased zinc intake is caused by hyperglycaemia-induced high expression of zinc receptors. Zinc is an intracellular signalling molecule, able to convert extracellular impulses to intracellular processes and to mediate interaction between cells).
- Up-regulation of urokinase plasminogen activator (uPA), a critical mediator in cancer cells displacement.
- Stimulation of ETM (epithelial to mesenchymal transition) process, a mechanism that enables cancer cells to metastasise.

Moreover, hyperglycaemia induces epigenetic changes resulting in constant activation of oncogenic pathways, a

phenomenon called "hyperglycaemic memory". Activation of oncogenic pathways is regulated by overexpression of well-known neoplastic mediators, nuclear factor-κB (NF-κB) and neuregulin-1 (Nrg1) [44].

Role of Obesity and Fat-Induced Chronic Inflammation in Cancer Biology

Adipose tissue consists of adipocytes, endothelial, immune cells like and cytokines, associated with cancer risk and progression [21]. The vast majority of patients with T2DM are obese or overweight. Besides being a risk factor for T2DM and various cardiovascular disorders, obesity reveals pro-neoplastic activity [48–52]. Nowadays, the correlation between obesity and carcinogenesis has been widely discussed. It was reported that adiposity promotes the development of breast, endometrial, pancreatic, colorectal and oesophageal cancer [48–49]. Meta-analysis of case-control and prospective cohort studies has confirmed that T2DM is an independent risk factor for the development of non-Hodgkin lymphoma, and cancer of the bladder, breast, colon and rectum, endometrium, liver and pancreas [48], and some studies report that nearly 40% of all cancers can be attributed to overweight and obesity [49]. Obesity presumably exerts its pro-neoplastic activities in various ways. It interferes with sex hormones physiology, induces chronic inflammation and changes profile of adipose tissue polypeptide hormones (adipokines) [41, 49]. Adipose tissue is a crucial endocrine organ and in condition of abundance leads to dysregulation of endocrine mechanisms. Excessive adipose tissue expresses high amounts of aromatase, an enzyme critical in converting androgens to oestrogens, leading to high levels of oestrogens, which accompanied by low concentration of progesterone increases the risk of oestrogen-related breast and endometrial cancers [21, 41, 49]. Obesity-induced chronic inflammation is characterized by increased production of proinflammatory cytokines including interleukin-6, resistin and TNF-alpha (Tumour Necrosis Factor-alpha), which in turn lead to an increase in insulin levels, further increasing the inflammatory response [41]. Moreover, excessive adipose tissue secretes high amount of VEGF (Vascular Endothelial Growth Factor) and MMP (matrix metalloproteinases) leading to tumour growth and metastasis, respectively [41]. Adiponectin and leptin are two antagonist adipokines with significant impact on carcinogenesis [49, 50]. The level of adiponectin is decreased and the level of leptin is increased in patients with excessive adipose tissue. Adiponectin sensitizes cells to insulin, suppresses cells growth and metabolism, and exerts pro-apoptotic mechanisms, whereas leptin stimulates proliferation of cancer cells [49, 50]. In clinical studies, adiponectin inhibited tumour development in in vitro breast cancer cell lines and in animals afflicted by sarcomas [51, 52]. Conversely, leptin exacerbates insulin resistance and induces tumour-promoting processes, stimulates angiogenesis and tumour proliferation, and prevents apoptosis [49].

Diabetes and the Correlation with Oncogenesis in Particular Organs

Various studies emphasize that DM may induce neoplastic transformation [6]. Nevertheless, the exact influence of DM on carcinogenesis in particular organs has not been fully elucidated and the results of different studies remain conflicting. The positive correlation between DM and tumourigenesis was observed for organs of digestive system (pancreas, colon and liver), genitourinary system (bladder, kidney, endometrium), head and neck region and breast [53, 54]. On the other hand, a negative, inverse correlation was found only for prostate cancer which increases with increasing duration of diabetes [48]. The majority of the recent studies concern pancreatic and liver cancers; thus these two entities would be discussed more precisely than others. The current knowledge of the association between DM and cancers of particular organs is discussed below.

Pancreatic Cancer

The correlation between DM and increased risk of pancreatic cancer (PaC) was confirmed by various studies [55]. However, the association between diabetes and PaC remains unclear, because of a two-way relationship. PaC may lead to increased glucose and insulin levels followed by abnormal glucose metabolism, and abnormal glucose metabolism may cause neoplastic transformation in pancreatic cells. Huxley et al. reported a 50% increased risk of PaC in patients with T2DM history shorter than 5 years [56] and Elena et al. suggested that persons with diabetes have a 40% higher risk of PaC than people without diabetes [57]. In this study, the highest level of risk was observed in patients with DM lasting for 2–8 years; DM of 9 or more years was not associated with increased risk of PaC and may be possibly caused by hypoinsulinaemia that develops along with diabetes duration [57]. Conversely, an elevated risk of PaC in patients with long-lasting DM was reported in another study [58]. It has also been shown that patients with obesity and T2DM have a 54% higher risk of PaC [57]. On the other hand, Grote et al. observed a statistically significant increased risk of PaC in patients with HbA (1c) ≥6,5% compared with ≤5,4%, independently of obesity or insulin resistance [59]. It was found that patients with diabetes and T2DM have a higher propensity to suffer from PaC because of high serum concentration of insulin and its precursors. The authors did not find a significant association between T1DM and PaC [59, 214]. On the other hand, another study reported a two-times higher risk of PaC in patients with

T1DM or MODY than in people without diabetes [60]. There are also studies implying genetic predisposition to PaC in individuals with diabetes [61, 62]. Interestingly, Prizment et al. checked 10 different SNPs (Single Nucleotide Polymorphisms) related to DM and found a positive association between PaC incidence and DM only for one of the examined SNPs—GCKR rs780094 (glucokinase gene which rises plasma fasting glucose level) [61]. Additionally, it has been shown that GCKR rs780094 is associated with a higher risk of T2DM and PSA-detected prostate cancer [63]. Another research examining the genetic susceptibility to PaC in diabetics found a higher PaC risk in patients with glucose-rising allele of MADD rs11039149, FTO rs8050136 and MTNR1B rs1387153 variants. The inverse association was observed for BCL11A rs243021 [62].

Liver Cancer: it was established that T2DM as well as T2DM-related metabolic disorders stimulate tumourigenesis in hepatic cells. Hepatocellular carcinoma (HCC) is the most frequently observed primary malignant cancer in the liver and is also commonly present in diabetics [64]. In 1986 Lawson reported for the first time the positive association between higher prevalence of HCC in diabetics [65] and other authors confirmed this finding [66, 67]. Besides being observed in diabetics, HCC frequently occurs in patients with non-alcoholic fatty liver disease (NAFLD) and in those with obesity and insulin resistance [67]. NAFLD is a condition commonly seen in individuals with T2DM and is critically correlated with adiposity. NAFLD as well as T2DM and obesity stimulates tumourigenesis in liver cells via various mechanisms including modified adipokines profile (increased leptin level and decreased adiponectin level), oxidative stress (imbalance between antioxidant and prooxidant factors) and lipotoxicity (malfunction or death of non-adipose tissue cells caused by accumulation of excess lipids). Through the portal circulation, the liver is exposed to high amounts of circulating insulin. Constantly high insulin levels, via elevated production of IGF-1, lead to multiplication and apoptotic suppression in hepatic cells [68]. According to a meta-analysis of 25 cohort studies, the incidence of HCC is significantly increased in both men and women with DM [66], and other authors reached to consistent conclusions [64, 65, 68]. It is difficult to establish whether T2DM is an independent risk factor for HCC or whether T2DM leads to HCC via induction of other liver disorders including NAFLD, steatosis, alcohol abuse, cirrhosis and HCV/HBV infections [63, 69]. Beyond these contributing factors, the association between DM and HCC remains unclear [1].

Colon/Colorectal Cancer: a variety of studies established that T2DM predisposes to colon and colorectal cancers (CRC). A meta-analysis conducted by Larsson et al. revealed that DM is a significant risk factor for CRC [70]. The relative risk among diabetics was approximately 30% higher than in non-diabetics and was similar in both genders and the overall mortality of CRC is approximately 1.5 times higher in diabetics than in non-diabetics [70]. The positive association between T2DM and colon/colorectal cancer was also described in another study which found that the incidence of cancer was similar in colon and in rectum, with no statistically significant difference between genders [71]. Another meta-analysis revealed a 1.22-fold higher relative risk of CRC in people with diabetes [54]. Similar results were reported in other studies [53, 72].

Bladder Cancer: according to current knowledge there is also a positive association between T2DM and oncogenesis in bladder cells [73, 74]. The association was observed for both female and male diabetics. Woolcott et al. found an increased risk of bladder cancer in patients with diabetes with higher levels of risk in females [75]. Conversely, Zhu et al. reported a statistically significant increased risk for bladder cancer in men with T2DM [76].

Kidney Cancer: the clear association between renal cell cancer (RCC) and DM has not been fully elucidated. Various studies reported conflicting results. A prospective study of women with T2DM conducted by Hee-Kyung et al. revealed increased risk of renal cell cancer (RCC) in this group [77]. Similar associations were described in Japanese men and in Czech diabetics [78, 79]. No such correlation was found in another study [80]. Qayyum et al. suggested that DM is not an independent risk factor of RCC, but when combined with obesity or hypertension, it increased the risk of RCC [81]. Another study did not confirm that DM is a risk factor for RCC; however it revealed an increased risk of death from RCC in diabetics [82].

Endometrial Cancer: a significant role of DM in endometrial carcinogenesis was emphasized by a number of authors and it was also strongly implied that DM is an independent risk factor of endometrial carcinogenesis [83]. Lindemann et al. established a three times increased risk of endometrial cancer (EC) in diabetic women [84]. Interestingly, the risk of EC is more than six times higher in obese diabetics in comparison with non-obese non-diabetics [38]. An investigation on the influence of elevated serum glucose level on EC development revealed that both elevated serum glucose level caused by impaired glucose metabolism and DM increased the risk of EC [85]. It was suggested that DM might predispose to EC via hyperinsulinaemia-dependent reduced levels of adiponectin and through obesity-related decreased concentration of SHBG. The reduced levels of SHBG lead to elevated bioavailable oestrogen and testosterone amounts and eventually stimulate endometrial oncogenesis [49–86].

Breast Cancer: the significant correlation between DM and the high risk of oncogenesis in breast tissues has been widely discussed in the literature and is now well established [87, 88].

The revealed causes of breast carcinogenesis in DM include [87–89]:

- activation of IR or IGF-R through IGF
- overexpression of IR in breast tissue
- activation of insulin-dependent IP3-K/AKT/mTOR pathway
- hyperglycaemia
- insulin-induced increased level of bioavailable IGF-1
- insulin-induced increased concentration of leptin
- insulin-induced reduced level of adiponectin
- insulin-induced reduced level of SHBG resulting in increased amount of bioavailable oestradiol

The correlation between DM and breast cancer is mainly observed in postmenopausal women [87]. Nondiabetic postmenopausal obese women with hyperinsulinaemia are at higher risk of BC incidence in comparison to normoinsulinemic ones [90]. The presumed inequalities in the prevalence of BC in post- and premenopausal diabetic females may be induced by different oestrogen concentrations (modified indirectly by insulin) observed in these populations [32].

The correlation between T2DM and BC incidence was also studied in MKR (MKR is a mouse model of T2DM, which has a genetically modified IGF-1 receptor) [91]. The authors of this study documented a positive relationship between BC and high insulin concentrations in MKR female mice with hyperinsulinaemia. The hyperinsulinaemic milieu in MKR led to proliferation and oncogenesis in breast cells. Subsequently, specimens of tumour and breast tissues from examined mice were taken for further research. The obtained tissues presented elevated level of IR and increased IR/IGF-1R activation that resulted in insulin-dependent metabolic effects and proliferation of mammary glands [91]. Overexpression of IGF-1R in breast tissue in transgenic mice and its influence on BC incidence was also emphasized in another study [92].

Head and Neck Cancers: studies investigating the association between DM and head and neck cancers (HNCs) are sparse with conflicting results. Some authors reported positive association, some reported negative inverse association and some found no correlation. The majority of precise studies focus on particular organs of the head and neck area. In general, the incidence of HNC was weakly associated with T2DM or no significant relationship was revealed [93, 94]. On the other hand, there is also the presumption that head and neck squamous cell carcinoma (HNSCC) is slightly inversely associated with T2DM [95].

Laryngeal Cancer

Japanese men with diabetes present a significantly higher risk of laryngeal cancer independently of smoking status [96]. Other studies on Japanese population of diabetics found an increased risk of laryngeal cancer in both genders [78, 97]. Conversely, the risk of laryngeal cancer incidence was decreased in a large group of U.S. veterans with T2DM [98]. No significant association between these two diseases was observed in another study [99].

Pharyngeal Cancer

A significantly higher risk of oropharyngeal and nasopharyngeal cancers was reported in Taiwanese individuals with T2DM [3]. The risk of pharyngeal cancer is higher in those with long-lasting T2DM in comparison to those with a short history of T2DM [99].

Oral Cancer

The increased risk of oral cancer incidence in diabetics has also been described [3, 99].

Prostate Cancer: according to the current knowledge, prostate cancer (PC) is the only neoplasm that is inversely related to DM [100], and a number of research documented a significant protective influence of DM on PC incidence [100–102]. This association is presumably a result of hyperglycaemia-induced low concentrations of testosterone and hypoinsulinaemia in patients with T1DM or long-lasting T2DM. Physiologically, insulin inhibits the hepatic synthesis of IGF-1-binding protein leading to increased bioavailability of IGF-1, which subsequently may induce prostate cells' proliferation. Hypoinsulinaemia in T1DM or long-lasting T2D consequently results in low circulating IGF-1 and suppresses prostate cells' multiplication.

Opposite results implying that DM promotes the development of advanced PC were found in a Japanese population where it was shown that people with diabetes aged 40–64 years had a significantly increased relative risk of PC incidence [103]. Men older than 40–64 years had also elevated PC risk, but the risk was lower than in younger patients [104].

Anti-diabetic Medications and Their Influence on Neoplastic Transformation

It was widely discussed that via intervening in mechanisms of cell cycle and cellular survival, anti-diabetic medications have a potential impact on carcinogenesis [6]. Presumably, the main linking factor between oncogenesis and anti-diabetic medications is in their capacity to stimulate insulin secretion or from exogenous administration. T2DM can be controlled by either oral or injectable medications, whereas T1DM is based on

multiple insulin doses. A number of studies have examined the role of anti-diabetics to increase or decrease the risk of cancer development or mortality and the effects of cancer therapy on insulin resistance and hyperglycaemia [105].

- Anti-diabetic medications decreasing insulin levels include:
  - metformin
  - thiazolidinediones (TZD)
- Anti-diabetic medications increasing insulin levels:
  - sulfonylureas
  - exogenous insulin
- Anti-diabetic medications decreasing insulin resistance include:
  - metformin
  - TZD

Hyperglycaemia and hyperinsulinaemia are well-known carcinogenesis-promoting factors; normalizing serum glucose and insulin concentrations may presumably prevent neoplastic transformation. Conversely, other studies have shown that glucose-lowering therapies do not increase the risk of cancer in patients with T2DM [106, 107]. The majority of studies on the association between anti-diabetic medications and oncogenesis concern metformin; thus, this drug will be discussed in detail.

Metformin: Mechanism of Action and Its Influence on Carcinogenesis

Metformin is a member of the biguanide family with activity as insulin sensitizer. Current recommendations consider metformin as a first-line medication for T2DM therapy [26, 108–110]. It is established that metformin suppresses oncogenesis through systemic (indirect, interfering in serum levels of glucose and insulin) and cellular (direct, targeted at tumour cells) mechanisms [32, 36, 111–121]. By comparison to normal cells, cancer cells tend to synthesize more ATP through glycolysis than normal cells [114]. This metabolic shift is a hallmark of cancer and facilitates the uptake and incorporation of more nutrients into nucleotides, amino acids and lipids required for highly proliferating cells [114].

Indirect Impact of Metformin on Neoplastic Transformation [6, 105, 113–120]

- Reduction of the serum glucose concentration via:
  - inhibition of hepatic gluconeogenesis (in LKB1/AMPK-dependent and/or -independent way).
  - inhibition of hepatic glycogenolysis by promoting hepatic adenosine monophosphate kinase phosphorylation
  - prevention of glucagon-dependent release of glucose from liver cells by accumulating AMP
  - suppression of gastrointestinal absorption of glucose
- Reduction of the serum insulin concentration.
- Suppression of inflammatory response by inhibiting the activation of NF-κB (*Explanation*: NF-κB is a critical factor in inflammatory response. Chronic inflammation stimulates oncogenesis [122–124]).
- Inhibition of metastatic progression by interfering in cancer stem cells biology (*Explanation*: Cancer stem cells are capable of undergoing epithelial to mesenchymal transition (EMT), a crucial process in metastasis, and a marker of unfavourable prognosis and cancer aggressiveness. Metformin is able to inhibit metastasis by damaging cancer stem cells [125–127]).
- Stimulation of the immune system, leading to CD8 T-cells production, by modifying fatty acid metabolism [128].
- Suppression of UPR (unfolded protein response) leading to activation of apoptosis [36].
- High local concentration of metformin after oral intake reduces the risk of oncogenesis (observed for colon cancer) [129].

Direct Impact of metformin on Neoplastic Transformation

- Reduction of ATP synthesis leading to inhibition of the formation of factors crucial for cancer cell survival.
- (*Explanation:*
- *Metformin → modifications in respiratory complex I → energetic stress → reduced production of ATP → activation of AMPK → inhibition of mTOR pathway → antiproliferative and energy saving mechanisms, inhibition of growth factor formation (insulin, IGF-1, glucose, leptin), inhibition of proteins and fatty acids formation)*
- Inhibition of mTOR pathway in AMPK-independent manner by decreasing insulin and IGF-1 concentrations.
- Activation of LKB1-dependent signalling resulting in suppression of oncogenesis (LKB1, *liver kinase B1*, is a well-known neoplastic suppressor).
- Reduction of the reactive oxygen species (ROS) formation.
- Suppression of VEGF, a critical factor of tumour vascularity formation.

- Suppression of HIF-1, a critical factor of tumour cells perseverance in hypoxic milieu.
- Cell cycle arrest and apoptosis induction via activation of cell cycle inhibitory components (p53, p21, cyclin D1).
- Modification of multidrug resistance 1 gene (MDR1 gene) and microRNA encoding P-glycoprotein (*Explanation*: Tumour cells are characterized by high expression of P-lycoprotein. Because of the fact that P-glycoprotein has the ability to eliminate hydrophobic chemotherapeutics from cancer cell, high concentration of P-glycoprotein in tumour cells reduces the effectiveness of chemotherapy).

Effects of Metformin on Neoplasms of the Digestive System

1. *Pancreatic cancer:* it has been shown that patients taking metformin have significantly decreased risk of pancreatic cancer by comparison to non-users and in those on insulin administration [130, 131].
2. *Liver cancer:* the risk of liver cancer is also significantly reduced in diabetics on metformin therapy [132, 133].
3. *Colorectal cancer:* researches examining the effect of metformin on colorectal cancer presented conflicting results. Whereas some of them observed a protective activity of metformin on CRC, others reported opposite outcomes [133–135].

Effects of Metformin on Neoplasms of the Genitourinary System

1. *Prostate cancer:* It was established that anti-diabetic therapy based on metformin reduces the risk of prostate cancer (up to 44% reduction in Caucasians) [136]. Other studies consistently reported a decreased risk of prostate cancer in metformin users [137, 138]. Interestingly, metformin users had also significantly a lower risk of advanced prostate cancer. The anti-neoplastic effect of metformin increased with the duration on metformin therapy [139].
2. *Kidney cancer:* In vitro studies on human kidney cancer cell lines 786-O revealed that metformin-mediated increased expression of microRNA-26a, a regulatory RNA critical in cell diversification, led to suppression of 786-O cells proliferation and oncogenesis [140].
3. *Ovarian cancer:* Various authors described that metformin reduced the risk of ovarian cancer incidence in women with T2DM undergoing metformin therapy. Metformin also improved overall survival and extended disease-free period in females with ovarian cancer [141, 142]. An in vitro study conducted on epithelial ovarian cancer cell lines OVCAR-3 and OVCAR-4 documented metformin-mediated anti-oncogenic results. Moreover, chemotherapy for ovarian cancer revealed better anti-neoplastic effects of cisplatin when enriched with metformin usage [143].
4. *Breast cancer:* Besides being helpful in chemotherapy for ovarian cancer, metformin revealed its usefulness in chemotherapy for breast cancer. Metformin was able to damage BC stem cells refractory to chemotherapy based on doxorubicin. Such treatment schedule enabled destruction of BC stem cells (using metformin) and BC non-stem cells (using doxorubicin) [98]. Metformin also improved anti-neoplastic effects of chemotherapy for BC based on trastuzumab and on taxane [144, 145].

Effects of Metformin on Lung Cancer

It has been shown that the use of metformin may lead up to a 45% decrease in the incidence of lung cancer [146]. Metformin enhanced the effectiveness and final outcomes of chemotherapy for advanced non-small cell lung cancer (NSCLC) in individuals with T2DM [147].

Effects of Metformin on Head and Neck Cancers

According to sparse studies on the association between metformin and HNSCC in individuals with T2DM, metformin may presumably reduce the risk of HNSCC incidence. A statistically significant decrease was observed for nasopharyngeal and oropharyngeal cancers [148]. This anti-diabetic drug was also able to suppress the proliferation of HNSCC cells, and to decrease the probability of HNSCC recurrence and metastasis [149, 150]. It led to better overall condition in diabetics with HNSCC, especially in those with laryngeal cancer [151]. On the other hand, there is also a report of no substantial interference of metformin on the HNSCC risk in diabetics [95].

Sulfonylureas: Mechanism of Action and Influence on Carcinogenesis

The most important sulfonylureas used as anti-diabetic medications are Glyburide, Glimepiride and Glipizide. Their main mechanism of action is regulation of insulin secretion by closing the potassium channel located in pancreatic β

cells. Sulfonylureas-induced potassium channels closure results in elevated insulin efflux and increased postprandial and fasting insulin levels. Whereas potassium channels closure presumably induce anti-tumourigenic mechanisms, sulfonylureas-stimulated hyperinsulinaemia promotes tumourigenesis [152]. Nevertheless, the exact effect of sulfonylureas on oncogenesis and cancer biology has not been fully elucidated [153]. The results of various studies on this issue remain conflicting. In addition, particular sulfonylureas presumably have different influence on carcinogenesis. Significantly elevated risk of cancer incidence in individuals with T2DM undergoing sulfonylureas therapy was reported by a variety of authors [135, 154, 155]. Diabetics on sulfonylureas had an increased risk of liver and colon cancer and decreased risk of prostate cancer [155, 156]. According to clinical reports, gliclazide was able to reduce the risk of neoplasm development in diabetics, whereas glyburide reduced the risk in some studies, and increased in others [157–159]. Until today, the relationship between glimepiride, glipizide and oncogenesis has not been established [158].

Exogenous Insulin: Influence on Carcinogenesis

The group of exogenous insulins comprise human insulin and insulin analogues. The vast majority of studies investigating the association between exogenous insulin and oncogenesis imply tumour-promoting effects of exogenous insulin [154, 160]. Patients on long-acting insulin analogues (glargine and detemir) are more prone to undergo carcinogenesis in comparison to non-insulin users [113, 161]. Nevertheless, the risk is lesser than observed in human insulin users [162]. Diabetics on insulin revealed increased risk of liver, pancreatic, renal, stomach, liver and respiratory tumours, and reduced risk of prostate cancer [156, 163]. Studies focusing on glargine effect on cancer biology present conflicting results. Diabetics on glargine had increased risk of breast, prostate and pancreatic cancers incidence and reduced risk of colon and colorectal cancers [164–166]. Glargine investigations in vitro have shown suppressed apoptosis and tumour-promoting activity in human endometrioid endometrial carcinoma, breast adenocarcinoma and CRC cells [167–169]. No significant correlation between glargine and oncogenesis was observed in another study [170].

Thiazolidinediones: Mechanism of Action and Influence on Carcinogenesis

Thiazolidinediones are a group of PPARγ agonists currently used in T2DM treatment. The main components of this group are Pioglitazone, Rosiglitazone, Troglitazone, Netoglitazone, Ciglitazone and Efatutazone. TZD-induced stimulation of PPARγ sensitizes insulin-dependent tissues to insulin that leads to better glycaemic regulation. The speculation that TZD may presumably have an impact on cancer biology was made after finding that a variety of neoplasms are characterized by elevated expression of PPARγ. Nevertheless, the possible influence of TZDs on oncogenesis may be induced in PPARγ-dependent and PPARγ-independent manner. TZD-mediated activation of PPARγ in cancer cells interfered with cell cycle and led to cell cycle arrest and apoptosis [171].

PPARγ-independent anti-neoplastic activity of TZD [171, 172]:

- Suppression of antiapoptotic Bcl-2 (B-cell leukaemia/lymphoma)/Bcl-xL function resulting in apoptosis of cancer cells
- Inhibition of androgen activation by interfering in gene encoding androgen receptor
- Degradation of specificity protein 1 (Sp1) resulting in reduction of survivin (an apoptosis inhibitor), EGFR (epidermal growth factor), and intercellular and vascular cell adhesion molecules ICAM-1 and VCAM-1
- *(Explanation*: Specificity protein 1 is a critical protein in cell cycle. This protein is able to modify genes encoding cell cycle and vascular endothelial growth factor. Such ability enables Sp1 to interfere with development, metabolism and metastasis of cancer cells.)
- Down-regulation of various well-established cancer-promoting molecules including β-catenin, cyclin D1 and FLIP (FLICE-like inhibitory protein)

The majority of studies suggested that TZDs have anti-neoplastic activity and reduces the risk of various cancers incidence [155, 173, 174]. On the other hand, there are reports indicating that these drugs may also reveal tumour-promoting features. It was observed that TZDs as a group decreased the risk of breast, lung and colorectal cancers [175]. Pioglitazone and rosiglitazone were able to reduce the risk of liver cancer, pioglitazone but not rosiglitazone reduced the risk of breast cancer and rosiglitazone reduced the risk of colorectal cancer [174, 176]. Netoglitazone revealed anti-neoplastic activity against human pancreatic cancer cells, colorectal cancer cells, multiple myeloma and prostate cancer cells (mainly androgen-irrespective prostate cancer cells) [177–179]. Efatutazone suppressed colon cancer development in mice and suppressed in vitro anaplastic thyroid carcinoma cell lines [180]. Suppressed proliferation of ovarian, prostate and lung cancer cells was observed after Troglitazone administration [180]. Possibly, TZDs may also improve the efficacy of chemotherapy. Chemotherapy for breast and pancreatic cancer cells was improved after rosiglitazone administration. Rosiglitazone presumably reduced chemoresistance in neoplastic cells [181]. Additionally, TZDs enhanced the effectiveness of anti-neoplastic therapy for soft tissue sarcoma and thyroid cancer [182].

On the other hand, there are also studies implying that TZDs as a group may induce pro-neoplastic effects. Such significant correlation was found in diabetic women undergoing rosiglitazone treatment [183]. Several studies suggested that diabetics on Pioglitazone therapy had increased risk of bladder cancer, NHL and melanoma [22, 184–187].

Incretin-Based Medications: Mechanisms of Action and Influence on Carcinogenesis

Dipeptidyl peptidase-4 inhibitors (DDP-4-i) and Glucagon-like peptide 1 agonists (GLP-1 agonists) are anti-diabetic medications used in T2DM that interact with the incretin system.

Dipeptidyl Peptidase-4 Inhibitors (DDP-4-i) include Sitagliptin, Saxagliptin, Vildagliptin, Alogliptin and Linagliptin. Dipeptidyl peptidase-4 inhibitors' main function is based on inhibiting the enzyme Dipeptidyl peptidase-4 (DDP-4) that is critical in destruction of Glucagon-like peptide-1 (GLP-1). Consequently, suppression of DDP-4 leads to increased serum concentration of GLP-1. Unlike GLP-1 agonists, DDP-4-i do not delay the gastric emptying rate and do not promote the sensation of satiety. A variety of studies found that DDP-4-i users were at higher risk to suffer from pancreatic cancer. However, the risk was significantly lesser than observed in diabetics on sulfonylureas and comparable in individuals on TZDs [188–191]. No pro-neoplastic activity of DDP-4-i was found in mice and in human individuals with T2DM [106, 192]. On the other hand, laboratory studies on rats revealed diminished colon tumourigenesis and reduced reactive oxygen species in long-term administration of Sitagliptin [193]. In addition, sitagliptin enhanced engraftment of Umbilical Cord Blood transplantation in adults with haematological neoplasms [194].

Glucagon-like Peptide 1 Agonists (GLP-1 agonists) include Liraglutide, Exenatide and Semaglutide. GLP-1 agonists elevate glucose-mediated insulin synthesis and its efflux in pancreatic β *cells in a precise and controlled way. They reduce glycogenolysis and glucagon secretion. GLP-1 agonists slow down the* gastrointestinal motility leading to delayed absorption of carbohydrates and lesser increase in serum glucose level [27]. Additionally, they promote satiety via interfering in the central nervous system. Whereas several studies found decreased risk of oncogenesis in GLP-1 agonist users, other research reported opposite results. Exenatide was able to suppress the development of human prostate cancer cells and murine CT26 colon cancer cells [195–196]. Moreover, it presented anti-neoplastic activity against breast cancer cells [197]. Liraglutide-induced stimulation of GLP-1R (GLP-1 receptors) suppressed neoplastic transformation and metastasis in human pancreatic cancer cells in in vitro and in vivo investigation. The anti-neoplastic activity was a result of suppression of PI3K/Akt pathway [198]. On the other hand, GLP-1 agonists elicited tumourigenesis in rodent thyroid C-cells, but not in human thyroid C-cells nor in thyroid gland in diabetics [199–200]. The proliferation observed in rodent C-cells might be caused by GLP-1-receptors–mediated excretion of calcitonin [201]. Presumably, mainly various levels of GLP-1 receptors in humans and in rodents caused this difference. There are also reports implying elevated risk of pancreatic cancer incidence in GLP-1 agonist users [189, 191].

Alpha-Glucosidase Inhibitors (AGIs)

Mechanisms of Action and Influence on Carcinogenesis: the main components of this group are Acarbose, Voglibose and Miglitol. AGIs slow down digestion and absorption of polysaccharides in the gastrointestinal tract by inhibiting enzymes sucrose (invertase) and maltase in the proximal small intestine, leading to delayed increase in postprandial serum glucose level and better glycaemic control. AGIs elevated intestinal hormones activity and enhanced intestinal microbiota [202]. Reports of the influence of AGIs on oncogenesis are scarce. According to current knowledge AGIs may reduce the risk of colorectal, lung and gastric cancers [203, 204]. The risk of kidney cancer is presumably elevated in diabetics undergoing AGIs therapy [205]. Conversely, no significant influence of AGIs on both carcinogenesis and cancer-related mortality was revealed in another study [206].

Sodium-Glucose Co-transporter 2 Inhibitors (SGLT2 Inhibitors)

Mechanism of Action and Influence on Carcinogenesis: SGLT2 inhibitors are a new class of anti-diabetic medications used in T2DM treatment. The main components of this group are Empagliflozin, Canagliflozin, Dapagliflozin and Ertugliflozin. SGLT2 is a glucose transporter located in the proximal renal tubules; their main role is glucose reabsorption of approximately 90% of the renal glucose filtrate. Consequently, SGLT2 inhibitors are able to significantly lower serum glucose levels via enhancing glucose excretion by the kidneys. Additionally, SGLT2 inhibitors elevate insulin sensitivity, improve insulin secretion from pancreatic beta cells and decrease gluconeogenesis [207]. As SGLT2 inhibitors are quite novel drugs the precise association between them and oncogenesis has not been completely established. Correlation between these two entities has already been observed, but it is still based on sparse research. Studies assessing the correlation between Dapagliflozin and bladder cancer have shown that Dapagliflozin might elevate the risk of oncogenesis in bladder cells, albeit without statis-

tical significance. No increase in neoplastic transformation in bladder tissue was found in mice and rats receiving Dapagliflozin, and for in vitro human bladder transitional cell carcinoma (TCC) cell lines [208]. Moreover, Dapagliflozin presumably did not increased the risk of breast cancer [208]. Studies about Canagliflozin have not documented an increased risk of neoplastic transformation in bladder, breast and kidneys [208]. Another study on SGLT2-expressing neoplasms (pancreatic and prostate cancers) found that Dapagliflozin and Canagliflozin significantly reduced tumour growth and enhanced death of tumour cells [209]. This finding should draw attention to the potential anti-neoplastic role of SGLT2 inhibitors in SGLT2-expressing tumours. Tumour-suppressing activity of Canagliflozin was also observed for prostate and lung cancer cells. The anti-neoplastic role in this study was presumably induced by inhibiting mitochondrial complex-I supported respiration that resulted in limitation of cellular proliferation [210]. Nevertheless, observations about the potential anti-neoplastic activities of SGLT2 inhibitors require further investigation.

Summary

The prevalence of diabetes mellitus type 2 and cancers of various sites is dramatically increasing nowadays. Both entities are important causes of death all over the world. A number of studies proved that DM increases the risk of oncogenesis in various organs. The association was predominantly observed in T2DM possibly because of potential T2DM-induced tumour-promoting factors. The mechanisms linking DM and neoplastic transformation in various types of organs are probably different and have not been clearly explained yet. The vast majority of attention is put on three groups of linking factors, including modifiable, non-modifiable and biological**.** Modifiable risk factors include overweight and obesity, physical inactivity, smoking and alcohol abuse. Non-modifiable risk factors comprise age between 55 and 60 years or more, male gender and African American race. Biological risk factors include hyperinsulinaemia, insulin resistance, hyperglycaemia and chronic inflammation induced by excessive adipose tissue. According to current knowledge the most significant factor linking T2DM and oncogenesis is obesity. Moreover, several studies suggest that there is also correlation between DM duration and the risk of carcinogenesis albeit the results of these investigations are inconsistent. It was established that many tumours overexpress receptors for insulin leading to higher susceptibility to both metabolic and mitogenic activity of insulin in tumour cells. Furthermore, diabetics with T2DM and coexisting neoplasm have worse disease-free and overall survival than patients with neoplasm but without T2DM. In accordance with collected data, individuals with DM are more prone to suffer from cancers of digestive tract system (liver, pancreatic, colon/colorectal cancers) and genitourinary system (bladder and endometrial cancers). Breast cancer is also more commonly observed in diabetic women than in non-diabetic ones. Correlation between DM and renal cancer and HNC is not clear. Data investigating the association between DM and HNC are lacking. Current knowledge implies that DM increases the risk of both oral cavity and pharyngeal neoplasms. It was also established that DM predisposes to perineural invasion in patients with oral squamous cell cancer. In addition, the prognosis in patients with oral cavity cancer and DM is worse than in those without DM. The relationship between DM and laryngeal cancer is inconsistent; some authors suggest an increased risk, some authors report a lower risk and some have not found a relationship between these diseases. Conversely, several studies have reported a protective, anti-neoplastic effect of DM on the risk of prostate cancer, with a significantly inverse association between PC and DM. This protective association is presumably a result of hyperglycaemia-induced low concentration of testosterone and hypoinsulinaemia in patients with T1DM or long-lasting T2DM. Nevertheless, other reports indicate an increased risk of prostate carcinogenesis. The potentially protective effect of DM on prostate cancer requires further investigation.

Recent analyses have shown that anti-diabetic drugs may modify the risk of oncogenesis in persons with diabetes, albeit with inconsistent results. Some drugs presumably increase the risk, whereas others reduce the risk of tumourigenesis. The majority of studies on this matter concern metformin, a drug of first choice in T2DM. It was been shown that metformin reduces the risk of cancer and improves the overall survival in diabetics. Favourable outcomes with the use of metformin have been observed in a wide variety of cancers including breast, pancreas, liver, colon, prostate, lungs and ovaries. Several authors have also revealed an inhibitory effect of metformin on human renal cancer cell lines 786-O. According to studies examining the influence of metformin on HNC, metformin decreased the risk of HNC (the most significant reduction was found for oro- and nasopharyngeal cancers) and improved overall survival in patients with laryngeal squamous cell carcinoma. It has also been suggested that SGLT2 inhibitors express potential anti-neoplastic activity, albeit the evidence is still sparse. The influence of other anti-diabetic medications including sulfonylureas, exogenous insulin, TZDs, alpha-glucosidase inhibitors, incretin-based drugs (GLP-1 agonists and DDP-4-i) on cancer incidence and prognosis remains inconsistent.

Based on the above information, it can be assumed that diabetes mellitus and oncogenesis are presumably combined entities. It is increasingly recognized that diabetes increases the risk of developing cancer [211]. Diabetes and cancer

commonly coexist and outcomes in people with both conditions are poorer than in those who have cancer but no diabetes [211]. Greater attention should be devoted to screen patients with diabetes mellitus for the main causes of cancer, especially those with T2DM. These patients require precise, regular follow-up in order not to omit any neoplastic transformation [211]. Careful screening should also be performed in individuals on anti-diabetic drugs [212].

The correlation between DM/anti-diabetic medications and carcinogenesis requires further investigation to establish exact, general and cell-intrinsic mechanisms linking these entities. Attention should also be drawn to potential anti-neoplastic activities of particular anti-diabetic drugs. Therapeutic nihilism should be avoided and a personalized approach to managing hyperglycaemia in people with cancer is required [211].

Concluding Remarks

- Diabetics (mainly with T2DM) are more prone to suffer from cancers of digestive tract system (liver, pancreatic, colon/colorectal cancers) and genitourinary system (bladder and endometrial cancers). Breast cancer is also more commonly observed in diabetic women than in non-diabetic ones.
- Prostate cancer risk is presumably inversely associated with diabetes mellitus.
- Metformin may reduce the risk of cancer incidence and improve overall survival in diabetics. Favourable effect of metformin was observed in a wide variety of cancers including breast, pancreatic, liver, colon, prostate, lungs and ovaries. Its potential usefulness in chemotherapy is promising and still studied.
- SGLT2 inhibitors express potential anti-neoplastic activity. The influence of sulfonylureas, exogenous insulin, TZDs, alpha-glucosidase inhibitors, incretin-based drugs (GLP-1 agonists and DDP-4-i) on cancer incidence and prognosis remains inconsistent.

Multiple-Choice Questions

1. The linking factors between diabetes mellitus and oncogenesis are:
   (a) Hyperglycaemia
   (b) Hypoinsulinaemia
   (c) Hyperinsulinaemia
   (d) **a, c**. (The biological factors linking DM and oncogenesis include hyperinsulinaemia, insulin resistance, hyperglycaemia and chronic inflammation induced by excessive adipose tissue. According to current knowledge the most significant factor linking T2DM and oncogenesis is obesity.)
   (e) a, b, c
2. Fat-induced chronic inflammation leading to oncogenesis is characterized by:
   (a) Increased level of adiponectin and decreased level of leptin
   (b) Increased level of leptin and decreased level of adiponectin
   (c) Increased production of proinflammatory cytokines including IL-6, resistin and TNF-alpha
   (d) **b, c. (**Excessive adipose tissue interferes with sex hormones physiology (high amounts of aromatase converting oestrogens to androgens), induces chronic inflammation and changes profile of adipose tissue polypeptide hormones (adipokines). Obesity-induced chronic inflammation is characterized by increased production of proinflammatory cytokines including interleukin-6, resistin and TNF-alpha (Tumour Necrosis Factor-alpha). The level of adiponectin is reduced and the level of leptin is increased in patients with excessive adipose tissue. Adiponectin sensitizes cells to insulin, suppresses cells growth and metabolism, and exerts pro-apoptotic mechanisms, whereas leptin stimulates proliferation of cancer cells.**)**
   (e) All answers are false
3. Pro-neoplastic features of insulin are induced by activation of:
   (a) Insulin Receptor
   (b) Insulin-like Growth Factor Receptor
   (c) Growth Hormone Receptor
   (d) a, b, c
   (e) **a, b. (**The pro-neoplastic features of insulin are induced by activation of its receptors (Insulin Receptor and Insulin-like Growth Factor Receptor), as well as via Insulin-like Growth Factor. Ligand-induced IR autophosphorylation triggers intracellular mechanisms. The most important one is activation of PI3K/Akt/mTOR (phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin) signalling pathway. Stimulation of PI3K/Akt/mTOR signalling pathway plays a critical role in oncogenesis. Activation of IGF-R results in more significant pro-neoplastic effects than activation of IR.)
4. Indirect effects of hyperinsulinaemia on cancer biology:
   (a) **Increased level of Growth Hormone (GH) leading to elevated concentration of Insulin Like Growth Factor-1 (IGF-1). (**Insulin stimulates growth hormone receptors (GHR) located in the liver leading to elevated release of GH. Subsequently,

GH promotes IGF-1 synthesis. IGF-1 is a mitogenic factor.)

(b) Increased concentration of pro-neoplastic adipose tissue hormone—adiponectin
(c) Increased concentration of anti-neoplastic adipose tissue hormone—leptin
(d) a, b, c
(e) All answers are false

5. Tumour-promoting mechanism of hyperglycaemia:
   (a) Reduced expression of glucose transporters (GLUT-1 and GLUT-3)
   (b) Reduced level of hypoxia-inducible factor α (HIF-α), a critical anti-neoplastic factor
   (c) **Increased expression of PPAR α and γ (peroxisome proliferator-activated receptor)** (PPAR α and γ interfere with lipid metabolic pathways and speed up neoplastic cells development)
   (d) a, b, c
   (e) b, c
6. Which statements are correct:
   (a) Diabetes mellitus type 2 elevates the risk of endometrial cancer
   (b) Diabetes mellitus type 2 elevates the risk of prostate cancer via reducing testosterone levels
   (c) The risk of hepatocellular carcinoma is increased in patients with type 2 diabetes mellitus
   (d) a, b, c
   (e) **a, c.** (It is suggested that DM might predispose to EC via hyperinsulinaemia-dependent reduced level of adiponectin and via obesity-related decreased concentration of SHBG. Reduced level of SHBG leads to elevated bioavailable oestrogen and testosterone amounts and eventually stimulates endometrial oncogenesis

      Liver is exposed to circulation of high amounts of insulin because of its portal vessels. Constantly high insulin levels, via elevated production of IGF-1, lead to multiplication and apoptosis suppression in hepatic cells.

      According to current knowledge prostate cancer (PC) is the only neoplasm that is conversely related to DM. This association is presumably a result of hyperglycaemia-induced low concentration of testosterone and hypoinsulinaemia detected in T1DM or long-lasting T2DM.)
7. Anti-neoplastic features of metformin comprise:
   (a) Reduction of the serum insulin concentration
   (b) Reduction of the serum glucose concentration via inhibition of gluconeogenesis and glycogenolysis in the liver
   (c) Stimulation of mTOR pathway, a critical anti-neoplastic pathway
   (d) a, b, c
   (e) **a, b (answer c is false because metformin** inhibits mTOR pathway in AMPK-independent manner by decreasing insulin and IGF-1 concentrations. mTOR pathway plays a critical role in oncogenesis).
8. Choose the correct statement:
   (a) Metformin reduces the risk of liver cancer
   (b) Metformin reduces the risk of pancreatic cancer
   (c) Metformin reduces the risk of ovarian cancer
   (d) **All answers are correct**
   (e) All answers are false
9. Anti-diabetic medications that influence the risk of neoplastic transformation are:
   (a) Metformin
   (b) Thiazolidinediones
   (c) Sulfonylureas
   (d) Dipeptidyl peptidase-4 inhibitors
   (e) **a, b, c, d.** (A majority of studies present that metformin reduces the risk of neoplastic transformation. The influence of sulfonylureas, thiazolidinediones and dipeptidyl peptidase-4 inhibitors on cancer incidence and prognosis remains inconsistent.)
10. Diabetes mellitus type 2 promotes oncogenesis via:
    (a) Activation of insulin-dependent IP3-K/AKT/mTOR pathway
    (b) Insulin-induced increased level of bioavailable IGF-1
    (c) Insulin-induced increased concentration of leptin
    (d) Insulin-induced reduced level of SHBG resulting in increased amount of bioavailable oestradiol
    (e) **a, b, c, d**

Glossary

Hyperinsulinaemia Increased serum insulin level.
Hyperglycaemia Increased serum glucose level.
Pro-neoplastic Promoting neoplastic transformation.
PI3K/Akt/mTOR signalling pathway (phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin signalling pathway)— Critical pathway in oncogenesis.
IGF-binding proteins Proteins crucial in IGF serum transfer and bioavailability.
Urokinase plasminogen activator (uPA) A critical mediator in cancer cell displacement.
ETM (Epithelial to Mesenchymal Transition process) A mechanism that enables cancer cells to metastasise.
Adipokines Adipose tissue polypeptide hormones, e.g. leptin, adiponectin.
SNPs (Single Nucleotide Polymorphisms) A sequence in a single nucleotide that is observed at a specific position in the genome.

NAFLD (non-alcoholic fatty liver disease) A condition of fat deposits accumulation not induced by alcohol abuse. NAFLD is associated with metabolic syndrome and insulin resistance.

Lipotoxicity Malfunction or death of non-adipose tissue cells caused by accumulation of excessive lipids.

Oxidative stress Imbalance between antioxidant and pro-oxidant factors.

Oncogenesis, tumourigenesis, carcinogenesis A group of mechanisms leading to transformation of normal cells to cancer cells.

Milieu A setting in which something happens (environment, surrounding).

Gluconeogenesis A process of glucose biosynthesis.

Glycogenolysis A process of biochemical degradation of glycogen to glucose.

NF-κB A factor controlling transcription of DNA and cells survival.

OVCAR Epithelial ovarian cancer cell lines.

Stem cell Undifferentiated cells which have the ability to differentiate into specialized cells, and to divide to synthesize more stem cells.

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Wojciechowska J, Krajewski W, Bolanowski M, Krecicki T, Zatonski T. Diabetes and Cancer: a Review of Current Knowledge. Exp Clin Endocrinol Diabetes. 2016;124(5):263–75. *A review article written by the authors of this chapter. The chapter is based on this article. The article, similarly to this chapter, analyse the association between diabetes mellitus (mainly type 2 diabetes mellitus) and cancer risk and cancer biology. The article also present the association between diabetes mellitus and antidiabetic medications*

Wu L, Zhu J, Prokop LJ, Murad MH. Pharmacologic therapy of diabetes and overall cancer risk and mortality: a meta-analysis of 265 studies. Sci Rep. 2015;5:10147. *A meta-analysis assessing the association between anti-diabetic pharmacotherapy and cancer risk and mortality*

Part X

Diabetes in Special Populations

Diabetes in Children and Adolescents

64

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Objectives

- To identify the types of diabetes mellitus that can affect children and adolescents.
- To provide information about diagnostic tests for identifying the etiology of diabetes mellitus in children and adolescents.
- To describe the epidemiology, risk factors, clinical presentation, treatment, and follow-up for comorbidities in pediatric patients with type 1 and 2 diabetes.

Introduction

Diabetes mellitus is one of the most common chronic diseases in pediatric patients. The prevalence of diabetes in adolescents from 12 to 19 years of age in the United States during 2005–2014 was 0.8%, of which 28.5% was undiagnosed, and the prevalence of prediabetes was 17.7% [1].

Several decades ago, type 1 diabetes was considered to occur only in children; and T2D, only in adults. However, the proportion of adult patients with type 1 diabetes and the incidence of T2D in children and young adults have been increasing. Given the current obesity epidemic, distinguishing between type 1 and 2 diabetes in children can be difficult. Currently, excessive weight is common in children with type 1 diabetes, whereas autoantibodies and ketosis may be present in patients with T2D. However, the identification of the type of diabetes is important for the choice of treatment, educational approach, nutritional program, and prevention of complications.

The care and management of children and adolescents with diabetes have unique aspects such as the following: (1) changes in insulin sensitivity related to growth and sexual development; (2) dependency care; and (3) neurological susceptibility to changes in glucose levels. A multidisciplinary team of specialists in pediatric diabetes should provide care to these patients. Family and individual management education are important for achieving a balance between adult supervision and independent self-care [2].

Definition and Diagnostic Tests for Diabetes in Children

The term *diabetes mellitus in children* describes a group of disorders of abnormal carbohydrate metabolism that result in hyperglycemia in patients ≥10 and <18 years of age [3]. The diagnostic criteria for diabetes mellitus and increased risk of diabetes (prediabetes) of the Expert Committee of the American Diabetes Association are essentially the same in children and adults [4].

Diagnostic Tests for Diabetes

- Measurement of fasting plasma glucose levels ≥126 mg/dL with no caloric intake for at least 8 h.[1]
- Measurement of 2-h plasma glucose levels ≥200 mg/dL during an oral glucose tolerance test using a glucose load containing 1.75 g of anhydrous glucose per kilogram of body weight dissolved in water, with a maximum of 75 g of anhydrous glucose (footnote 1).

[1]In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

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- Measurement of HbA1c levels ≥6.5% using a method certified and standardized to the Diabetes Control and Complications Trial assay.* Marked discordance between the measured HbA1c and plasma glucose levels should raise the possibility of assay interference. In conditions such as hemoglobinopathies, pregnancy, glucose-6-phosphate dehydrogenase deficiency, HIV, hemodialysis, recent blood loss, or transfusion or erythropoietin therapy, HbA1c should not be used to diagnose diabetes. However, the studies that formed the basis for this recommendation included only adults, and whether the same HbA1c cutoff point should be used to diagnose diabetes in children and adolescents remains unclear. The American Diabetes Association has suggested that this criterion underestimates the prevalence of prediabetes and diabetes in obese children and adolescents [4–6].
- Measurement of random plasma glucose levels ≥200 mg/dL in a patient with classic symptoms of hyperglycemia or hyperglycemia crisis.

Diagnostic Tests for Increased Risk of Diabetes (Prediabetes)

- Impaired fasting glucose test: fasting plasma glucose levels of 100–125 mg/dL
- Impaired glucose tolerance test: 2-h plasma glucose levels of 140–199 mg/dL during an oral glucose tolerance test
- HbA1c analysis: 5.7–6.4% [4]

Etiological Classification

Distinguishing among the types of diabetes in all groups at onset has difficulties, and the true diagnosis becomes more obvious over time. The diabetes mellitus classification of the American Diabetes Association, which depends on causation, distinguishes the following types [4]:

- **Type 1 diabetes mellitus.** This is characterized by an absolute insulin deficiency, usually as a result of the autoimmune destruction of pancreatic beta cells (type 1A) or secondary to defects in insulin secretion from inherited defects in pancreatic beta cell glucose sensing (type 1B).
- **T2D mellitus.** This is characterized by insulin resistance resulting from defects in the action of insulin on its target tissues and is associated with varying and usually progressive failure of beta cell secretion.
- **Genetic defects of beta cell function (monogenic diabetes).** This type of diabetes is characterized by impaired insulin secretion by pancreatic beta cells caused by a single gene mutation. This genetically heterogeneous group includes the following: neonatal diabetes, mitochondrial diabetes, and maturity-onset diabetes of the young (MODY). These forms of diabetes represent <5% of patients with diabetes and are generally characterized by onset before the age of 25 years. The diagnosis of monogenic diabetes should be considered in children with the following conditions [7–10]:
  - Diabetes in the first 6 months of life
  - A family history of diabetes in first-degree relatives who lack the characteristics of type 1 diabetes (no islet autoantibodies, low or no insulin requirements >5 years after diagnosis [stimulated C-peptide level >200 pmol/L]) [9]
  - Strong family history of diabetes but without typical features of T2D (nonobese and low-risk ethnic group)
  - Mild fasting hyperglycemia (100–150 mg/dL), especially if young and nonobese
  - Children with diabetes not characteristic of type 1 or 2 diabetes that occurs in successive generations (suggestive of an autosomal dominant pattern of inheritance)
  - A prolonged honeymoon period of >1 year or an unusually low requirement of insulin (<0.5 U/kg/day) after 1 year of diabetes

    Neonatal diabetes. This rare disorder has an incidence of 1:300,000–1:400,000 live births [11]. It presents in the first 6 months of life and can be either transient or permanent. All children diagnosed with diabetes in the first 6 months of life should undergo immediate genetic testing for neonatal diabetes [4]. In patients diagnosed between 6 and 12 months of age, testing for neonatal diabetes mellitus should be limited to those without islet antibodies, as most patients in this age group have type 1 diabetes [9]. Almost 50% of cases are permanent, and the most common cause is an autosomal dominant defect in *KNJ11* or *ABCC8*, which encode the Kir6.2 and SUR1 subunits of the ATP-sensitive potassium channel, respectively. However, other genetic defects include the following [4, 12]:

    KCNJ11. Autosomal dominant inheritance. It causes a permanent or transient form. Clinical features include intrauterine growth restriction, possible developmental delay, and seizures and response to sulfonylureas.

    INS. Autosomal dominant inheritance. This is a permanent form of neonatal diabetes associated with intrauterine growth restriction and controlled with insulin.

ABCC8. Autosomal dominant inheritance. It causes a permanent or transient form. Patients usually have intrauterine growth restriction, rare developmental delay, and response to sulfonylureas.

6q24 (*PLAG1, HYMA1*). The inheritance is autosomal dominant. Mechanisms include uniparental disomy of chromosome 6, paternal duplication, or maternal methylation defect. It is a transient form. The clinical features are intrauterine growth restriction, macroglossia, and umbilical hernia. It may be treatable with medications other than insulin therapy.

GATA6. Autosomal dominant inheritance. It is a permanent form with pancreatic hypoplasia, cardiac malformations, pancreatic exocrine insufficiency, and insulin requirement.

EIF2AK3. Autosomal recessive inheritance. It is a permanent form of neonatal diabetes. It is known as Wolcott-Rallison syndrome, which includes epiphyseal dysplasia, pancreatic exocrine insufficiency, and insulin requirement.

EIF2B1. Autosomal recessive inheritance. It causes a permanent form and can be associated with fluctuating liver function.

FOXP3. X-linked inheritance. It is a permanent form. The clinical features include immunodysregulation, polyendocrinopathy, enteropathy X-linked syndrome (autoimmune diabetes, autoimmune thyroid disease, and exfoliative dermatitis), and requires insulin for treatment.

Patients with the permanent forms could be treated with sulfonylureas rather than insulin. Sulfonylureas trigger beta cell membrane depolarization, electrical activity, calcium influx, and insulin release. Patients with neonatal diabetes require 0.5 mg/kg/day on average, although some patients may need higher doses of up to 2.3 mg/kg/day [4, 13].

Mitochondrial diabetes. Some mitochondrial DNA mutations are strongly associated with diabetes, with the most common mutation being the A3243G mutation in the mitochondrial DNA-encoded tRNA gene. A gradual development of pancreatic beta cell dysfunction upon aging, rather than insulin resistance, is the main mechanism of glucose intolerance development. This mutation affects insulin secretion and may involve an attenuation of cytosolic ADP/ATP levels, which leads to a resetting of the glucose sensor in the pancreatic beta cells. Unlike MODY-2, mitochondrial diabetes shows a pronounced age-dependent deterioration of pancreatic function. In clinical practice, mitochondrial diabetes is suspected when a strong familial clustering of diabetes is present. Mitochondrial diabetes can be discriminated from MODY based on the presence of maternal transmission in conjunction with a bilateral hearing impairment in most carriers, although the final proof is provided by genetic analysis [14].

MODY. This is the most common form of monogenic diabetes and is caused by the autosomal dominant transmission of a genetic defect in insulin secretion. It is characterized by impaired insulin secretion with minimal or no defects in insulin action. The clinical characteristics of patients are heterogeneous, and MODY is often misdiagnosed as type 1 or 2 diabetes mellitus. MODY has many subtypes (Table 64.1). MODY-2 is the most common type occurring during childhood, and MODY-3 is the most common type after puberty [15, 16].

MODY should be considered in the following situations [7, 8]:

- Individuals with mild stable fasting hyperglycemia.
- Multiple family members with diabetes without type 1 characteristics (no islet autoantibodies and low or no insulin requirements 5 years after diagnosis) or T2D (marked obesity and acanthosis nigricans).

In the above-mentioned situations, children and those diagnosed in early adulthood with diabetes not characteristic of type 1 or 2 that occurs in successive generations should have genetic testing for MODY [4]. These individuals should be referred for further evaluation and genetic testing confirmation. Some forms of MODY, such as *HNF1A* and *HNF4A*, are sensitive to sulfonylureas. Mild fasting hyperglycemia due to CGK is not progressive during childhood, does not develop complications, and does not respond to low-dose insulin or oral agents, so these patients should not receive treatment [4, 7].

Genetic defects in insulin action. There are rare genetic abnormalities in the insulin receptor or signal transduction. One of them is Donohue syndrome (leprechaunism), a genetic autosomal recessive disorder that results from the presence of homozygous or compound heterozygous mutations in the insulin receptor gene (*INSR*; 19p13.3-p13.2). The incidence of this pathology is 1 in 1,000,000 births. The characteristics of this syndrome include severe intrauterine and postnatal growth retardation, multiple endocrine dysfunction, hypertrichosis, virilization, emaciation, acanthosis nigricans, lipoatrophy, genitomegaly, postprandial hyperglycemia, fasting hypoglycemia, insulin resistance, hyperinsulinemia, and eventual ketoacidosis. Infants with Donohue syndrome also have distinc-

Table 64.1 Classification of MODY (adapted from references [4, 7, 15])

MODY type	Gene and locus	Age at diagnosis	Primary defect	Associated features	Severity of diabetes
1	*HNF-4a* 20q	Post-puberty	Gene transcription defects in beta cells	Macrosomia and/or neonatal hypoglycemia. It is characterized by a progressive insulin secretory defect with presentation in adolescence or early adulthood. It is sensitive to sulfonylureas	Severe
2	*GCK* 7p	Childhood	Impairment of beta cell sensitivity to glucose and defect in hepatic glycogenesis	Reduced birth weight. This is the most common cause in the absence of symptoms or marked hyperglycemia. This is a stable form with nonprogressive elevated fasting blood glucose levels. Typically, it does not require treatment; microvascular complications are rare	Mild
3	*HNF-1a* 12q	Post-puberty	Similar to MODY-1	Renal glycosuria. This form occurs with a progressive insulin secretory defect with presentation in adolescence or early adulthood; decreased renal threshold for glucosuria; and marked increase in postprandial glucose levels. It is sensitive to sulfonylureas	Severe
4	*PDF1 (IPF-1)* 13q	Early adulthood	Defects in transcription factors during embryogenesis lead to abnormal beta cell development and function	–	Mild
5	*HNF-1b* 17cen-q21.3	Post-puberty	Similar to MODY-1 and MODY-3	Glomerulocystic kidney disease, female genital malformations, hyperuricemia, gout, abnormal liver function tests, and atrophy of the pancreas	Mild
6	*NeuroD1/ BETA2* 2	Early adulthood	Abnormal development and function of beta cells	–	Unknown
7	*KLFA11* 2p25	Early adulthood	Reduced glucose sensitivity of beta cells	Phenotype similar to T2D	Unknown
8	*CEL* 9q24	<20 years	Impaired endocrine and exocrine pancreatic function	Exocrine pancreatic dysfunction	Unknown
9	*PAX4* 7q32	<20 years	Impaired transcription of apoptosis- and proliferation-related genes in pancreatic beta cells	–	Diabetic ketoacidosis is possible
10	*INS* 11p15.5	<20 years	Loss of beta cell mass through apoptosis	–	Unknown
11	*BLK* 8p23	<20 years	Decreased insulin synthesis and secretion in response to glucose	Higher incidence in obese individuals	Unknown

tive characteristics, with elfin facies, low birth weight, skin abnormalities, and large, low-set ears. The diagnosis is based on a combination of typical dysmorphic characteristics and clinical evaluation supported by glycemic and insulin results and genetic analysis. The treatment of these patients is supportive and requires a multidisciplinary team. For instance, blood glucose levels may be maintained with frequent or continuous feeds and complex carbohydrates. Currently, treatment with recombinant insulin-like growth factor 1 has demonstrated effectiveness. The prognosis for this disorder is complicated and fatal; most fetuses with the disorder are either aborted or die within the first year of life [17].

- **Endocrinopathies.** Several hormones such as cortisol, growth hormone, epinephrine, and glucagon antagonize the action of insulin. Over-secretion of these hormones can result in glucose intolerance or diabetes mellitus [18].
- **Drug- or chemical-induced diabetes.** Drugs may induce hyperglycemia through different mechanisms, including alterations in insulin secretion and sensitivity, direct cytotoxic effects on pancreatic cells, and increases in glucose production. The drugs included in this list are antihypertensive drugs, lipid-modifying agents, protease inhibitors, nucleoside reverse transcriptase inhibitors, phenytoin, valproic acid, second-generation antipsychotics, antidepressant agents, glucocorticoids, chemotherapeutic agents, some oral contraceptives, growth hormone, and somatostatin analogs [19].
- **Cystic fibrosis-related diabetes.** Diabetes is the most common comorbidity in patients with cystic fibrosis, occurring in approximately 20% of adolescents and 40–50% of adults with cystic fibrosis. Insulin insufficiency is the primary defect, although genetically determined beta cell function and insulin resistance associated with infection and inflammation may also contribute.

Annual screening for cystic fibrosis-related diabetes with an oral glucose tolerance test beginning at age 10 years is recommended. HbA1c test is not recommended. Screening for cystic fibrosis-related diabetes should be performed using the 2-h (1.75 g/kg maximum 75 g) oral glucose tolerance test [20].

- Patients with cystic fibrosis should be treated with insulin. For patients with impaired glucose tolerance, prandial insulin therapy should be considered to maintain weight. Oral diabetes agents are not as effective as insulin in improving nutritional and metabolic outcomes in cystic fibrosis-related diabetes and are not recommended [20].
- Annual monitoring for complications of diabetes beginning 5 years after the diagnosis of cystic fibrosis-related diabetes is recommended [4].
- **Post-transplantation diabetes mellitus.** In this type of diabetes, individuals develop new-onset diabetes after transplantation. Patients should be screened after organ transplantation for hyperglycemia once they are stabilized with an immunosuppressive regimen and in the absence of an acute infection. Oral glucose tolerance test is the preferred diagnostic test [4].

The main types of diabetes mellitus are types 1 and 2, which will be discussed in detail below.

Type 1 Diabetes Mellitus

Epidemiology

Type 1 diabetes is one of the most common chronic diseases of childhood and affects males and females equally, with a slight male predominance in younger children. Type 1 diabetes has increased in recent years in both sexes, all age and race/ethnic subgroups, except for those with the lowest prevalence (age 0–4 years and American Indians) [21]. Globally, type 1 diabetes represents approximately 2% of the estimated total cases of diabetes, ranging from <1 to >15% [22]. The incidence and prevalence of type 1 diabetes mellitus vary according to the following factors:

- Age. The highest incidence occurs between 10 and 14 years of age [23].
- Season. Type 1 diabetes appears mostly in autumn and winter [23].
- Geographic location. The lowest incidence was reported in Pakistan and Venezuela (0.1 per 100,000 per year); and the highest incidence, in Finland and Sardinia [24].
- Racial and ethnic groups. In the United States, the highest prevalence was in white youths, and the lowest prevalence was in American Indian youths [21].

The incidence of type 1 diabetes mellitus has been increasing at an annual rate of approximately 2.8% [24]. The increasing incidence of type 1 diabetes in children across the world over a short period cannot be explained by genetic factors; environmental risk factors have been suggested to contribute to the increasing trend in its incidence. Several risk factors have been associated with type 1 diabetes mellitus (e.g., infections, dietary factors, air pollution, and vaccines); however, most have been inconclusive [25].

Pathogenesis of Type 1 Diabetes Mellitus

Type 1 diabetes is an autoimmune disease. The pathogenesis of type 1 diabetes begins with the appearance of beta cell autoimmunity, which is primarily directed against insulin, glutamic acid decarboxylase (GAD), or both. Subsequently, other autoantibodies against islet antigen-2, tyrosine phosphatase-like insulinoma antigen 2, or the ZnT8 transporter may also appear. Dysglycemia and the symptoms of diabetes appear later [10, 26].

The rate of beta cell destruction is quite variable, but it is usually faster in infants and children than in adults. Pediatric patients may present with ketoacidosis as the first manifestation of the disease; other patients have modest hyperglycemia, which may increase with infection or other stressors. By contrast, adults may retain sufficient beta cell function to prevent ketoacidosis and eventually become insulin dependent [4].

Progression to diabetes occurred in 14–44% of children with persistent single insulin autoantibodies or GAD autoantibodies within 10 years. The incidence of progression in children with multiple islet autoantibodies was 50–70% within 10 years and 84% within 15 years. The progression to type 1 diabetes was faster in children younger than 3 years, children with the human leukocyte antigen genotype DR3/DR4-DQ8, and girls [27, 28]. Although accepted screening programs for type 1 diabetes are lacking, screening for type 1 diabetes risk with islet autoantibodies is recommended as an option for first-degree family members of a proband with type 1 diabetes. Individuals who test positive will be counseled about the risk of developing diabetes [4, 29].

Type 1 diabetes includes the following stages [4, 29]:

- Stage 1. A presymptomatic stage with autoimmunity (multiple autoantibodies) with normoglycemia
- Stage 2. A presymptomatic stage with autoimmunity but with dysglycemia (impaired fasting glucose or glucose tolerance), or HbA1c levels of 5.7–6.4% or ≥10% increase in HbA1c level
- Stage 3. A symptomatic stage and new-onset hyperglycemia according to the standard diabetes criteria
- Stage 4. Long-standing type 1 diabetes

Genetic Risk Factors of Type 1 Diabetes Mellitus

The primary risk factor of beta cell autoimmunity is genetic and mainly occurs in individuals with HLA-DR3-DQ2 and/or HLA-DR4-DQ8 haplotypes. The region encoding HLA contributes approximately 50% of the genetic risk. Although non-HLA genetic factors have a slight individual effect, 58 genomic regions show substantial genome-wide evidence of a type 1 diabetes association. Some candidate genes with likely functional effects are *IL27*, *BAD*, *CD69*, *PRKCQ*, *CLEC16A*, *ERBB3*, and *CTSH* [26].

Environmental Risk Factors of Type 1 Diabetes Mellitus

The increase in the incidence of type 1 diabetes mellitus can be explained by changes in environment or lifestyle. A trigger from the environment in an autoimmunity-genetically susceptible individual is generally needed. These factors may be present in both the prenatal and postnatal life stages. Candidate triggers with the strongest evidence include maternal or postnatal enteroviral infection, older maternal age, infant weight gain, serious life events, overweight or increased height velocity, puberty, insulin resistance, and psychological stress. Other suggested triggers include the following: congenital rubella; cesarean section; higher birthweight; low maternal intake of vegetables; frequent respiratory or enteric infections; abnormal microbiome; early exposure to cereals, root vegetables, eggs, or cow milk; persistent or recurrent enteroviral infections; high glycemic load, fructose intake, dietary nitrates, or nitrosamines; and steroid treatment [30].

By contrast, evidence shows that higher omega-3 fatty acids are a postnatal protective factor, and higher maternal vitamin D intake or concentrations in late pregnancy, probiotics in the first month of life, and the introduction of solid food while breastfeeding after age 4 months have also been suggested to be protective factors [30].

Clinical Presentation

Children with type 1 diabetes typically present with symptoms of polyuria, polydipsia, and diabetic ketoacidosis. However, children often do not present with the classical signs and symptoms of diabetes. Physicians should be aware of other presentations such as the following: bedwetting in children who had no previous night bedwetting episodes, unintended weight loss, irritability and other mood changes, fatigue, weakness, blurred vision, candida diaper dermatitis, and vaginal yeast infection.

The prevalence of diabetic ketoacidosis in youths with type 1 diabetes is nearly 30%, and a higher prevalence has been associated with younger age at diagnosis, minority race/ethnicity, and low income [31]. The frequency of diabetic ketoacidosis at diagnosis ranges from 12.8 to 80% among countries. This variation may be explained, at least in part, by different levels of disease awareness and health-care provision [32].

Situations that cause diagnostic difficulties that may delay diagnosis include the following [33]:

- The hyperventilation of ketoacidosis may be misdiagnosed as pneumonia or asthma (cough and breathlessness distinguish these conditions from diabetic ketoacidosis).
- Abdominal pain associated with ketoacidosis may simulate an acute abdomen and lead to referral to a surgeon.
- Polyuria and enuresis may be misdiagnosed as a urinary tract infection.
- Polydipsia may be thought to be a psychogenic disorder.
- Vomiting may be misdiagnosed as gastroenteritis or sepsis (Codner limited care).

Management of Type 1 Diabetes Mellitus

Diabetes Self-Management Education and Support

All people with diabetes should participate in diabetes self-management education and receive support to obtain the knowledge and skills for diabetes self-care. The four critical time points to promote education skills are at diagnosis, annually, or when treatment targets are not met, in cases of medical, physical, or psychosocial complicating factors, and in transitions in life and care [34]. The treatment of patients with diabetes can only be effective if the family implements it. Health-care providers must be capable of evaluating individual and family psychosocial factors to overcome barriers to treatment plans. In addition, other people who participate in the patient's care must be involved. As a large portion of a child's day is spent in school, communication and cooperation with school personnel is essential for optimal diabetes management [2]. Optimal management of diabetes at school is a prerequisite for optimal school performance and the prevention of diabetes-related complications. Schools should facilitate prescribed medical interventions, including support of insulin administration, and manage appropriately the effects of low and high blood glucose levels according to parent and health-care team instructions [35].

Diabetes Education

Pediatric patients and caregivers should receive culturally sensitive and developmentally appropriate individualized diabe-

tes education [2]. Education is key to the successful management of diabetes and maximizes the effectiveness of diabetes treatment. Structured educational programs should be aimed at the patient's achievement of diabetes care goals, improved psychosocial adaptation, and enhanced self-efficacy, in addition to implementing measures of glycemic control.

Educational interventions shown to be effective include the following [36]:

- Clear theoretical psycho-educational principles
- Integration into routine clinical care
- Ongoing provision of individualized self-management and psychosocial support
- Involvement of the continuing responsibility of parents and other caregivers
- Making use of cognitive behavioral techniques most often related to problem-solving, goal setting, communication skills, motivational interviewing, family conflict resolution, coping skills, and stress management
- Utilizing new technologies in diabetes care as one of the vehicles for educational motivation

Glycemic Control

Sufficient glycemic control must be achieved to prevent diabetes-related complications; however, strict glucose levels carry the risk of hypoglycemia. Although young children were previously thought to be at risk of cognitive impairment after episodes of hypoglycemia, current data have not confirmed this notion. Hence, current standards recommend lowering glucose levels to the safest possible level to prevent chronic complications. The blood glucose and HbA1c goals for type 1 diabetes across all pediatric age groups are as follows [2, 8, 37]:

- Blood glucose goal range before meals: 90–130 mg/dL
- Bedtime/overnight: 90–150 mg/dL
- HbA1c level: <7%, with an emphasis on target personalization

Goals should be individualized, and lower goals may be reasonable if they can be achieved without excessive hypoglycemia. Blood glucose goals should be modified in children with frequent hypoglycemia or hypoglycemia unawareness. A higher HbA1c level <7.5% may be more suitable for youth who cannot identify symptoms of hypoglycemia, with hypoglycemia unawareness, without access to analog insulins, or who cannot monitor blood glucose regularly. Even less stringent HbA1c targets (e.g., <8%) may be recommended for children with a history of severe hypoglycemia, severe morbidities, or short life expectancy. On the contrary, a lower goal (HbA1c level of 6.5%) may be appropriate if achievable without excessive hypoglycemia, impairment of quality of life, and undue burden of care. A lower goal may also be appropriate during the honeymoon phase of type 1 diabetes [2, 8, 38].

Assessment of glycemic status (HbA1c or other glycemic measurement) should be performed at least two times a year in patients who meet treatment goals and at least quarterly in patients whose therapy recently changed or who do not meet glycemic goals [37].

Continuous glucose monitoring devices are rapidly improving diabetes management and could estimate the time in range as a useful metric of glycemic control. These devices report the number of days they are worn, the percentage of time they are active, and the mean glucose levels. The glycemic variability target recommended is ≤36%, with a target range of 70–180 mg/dL at >70%, <70 mg/dL at <4%, <54 mg/dL at <1%, >180 mg/dL at <25%, and >250 mg/dL at <5% [37, 39].

Blood Glucose Monitoring

Glucose monitoring enables patients, parents, and clinicians to evaluate the efficacy of current therapy, make treatment adjustments, and ensure that glucose levels are within the safe goal ranges [40, 41]. Glucose monitoring allows decisions about the insulin dose in patients with intensive management. Sleep is a time of particular risk for severe and asymptomatic hypoglycemia; hence, overnight routine testing is recommended [42].

Increased daily frequency of self-monitoring of blood glucose levels is associated with lower HbA1c levels (−0.2% per additional test per day) and fewer acute complications. When children are old enough, they should be encouraged to auto-self-monitor their glucose levels. All children and adolescents with type 1 diabetes should self-monitor glucose levels up to 6–10 times/day with a glucometer or by continuous glucose monitoring, including prior to meals and snacks, at bedtime, and as needed (during exercise, when driving, and when symptoms of hypoglycemia occur) [2].

Capillary blood and continuous glucose monitoring enable patients to detect the impacts of diet, exercise, illness, stress, and medications on glucose levels. Both types of devices allow patients to recognize hypoglycemia and hyperglycemia. Continuous glucose monitoring has become a standard of care in patients with type 1 diabetes. The advantages of using this technology are the high number of glucose readings per day (up to 288), the alert provided when the blood glucose threshold has been crossed, and the impact on glucose levels (lower HbA1c level, less hypoglycemia, and more time and time in range). However, this benefit is mediated by adherence to sensor therapy, with at least 60% use being associated with these findings [33, 43, 44]. Intermittently scanned continuous glucose monitoring devices may also be available at lower costs than traditional meter-based testing, do not require calibration, and are safe for the pediatric population [44, 45].

Insulin Therapy

Patients with type 1 diabetes mellitus lack sufficient insulin to maintain normoglycemia. Intensive insulin regimens delivered by combinations of multiple daily injections or pump therapy with differential substitution of basal and prandial insulin to obtain optimal metabolic control has become the gold standard for all age groups in pediatric diabetology [46]. The insulin requirement is 0.25–0.5 units/kg/day for children 9 months–2 years of age, 0.5–0.6 units/kg/day for children between 1 and 6 years of age, 0.75 units/kg/day for children ≥7 years until the onset of puberty, and 0.75–1.5 units/kg/day for children starting puberty. For patients with diabetic ketoacidosis, the starting dose may be 1 unit/kg/day. Insulin dose adjustments are based on blood glucose [41]. Daily insulin dosage varies greatly between individuals and changes over time. It therefore requires regular review and reassessment [46]. The pharmacokinetic parameters of insulin commonly used in pediatric patients are shown in Table 64.2.

Intensive management with multiple-dose insulin and/or continuous subcutaneous insulin infusion in children and adolescents with type 1 diabetes mellitus showed marked declines in HbA1c level and chronic complications [47].

The primary goal of treatment is to mimic natural insulin secretion. To achieve this, patients require administration of the following [41, 42]:

1. Basal insulin to maintain near-normal blood glucose levels to prevent starvation between meals and suppress hepatic glucose production. Patients can use continuous subcutaneous insulin infusion or intermediate- or long-acting insulin to mimic basal insulin secretion.
2. Short-acting insulin to cover the carbohydrates consumed during meals and normalize blood glucose levels by intermittent injections based on glycemic corrections and carbohydrate foods throughout the day. As a normal daily diet includes three meals per day, short-acting insulin should be administered at least three times daily. Patients using this regimen need to establish the following parameters:
   - The units of rapid-acting insulin to be injected per gram of carbohydrates (insulin-to-carbohydrate ratio)
   - The amount of glucose that decreases with 1 unit of rapid-acting insulin (sensitivity factor)

Table 64.2 Pharmacokinetic parameters of insulin commonly used in pediatric patients (adapted from Beck and Cogen [41])

	Action profile		
Insulin	Onset	Peak	Duration
Rapid-acting			
Lispro	15–30 min	30–90 min	3–6 h
Aspart	10–20 min	40–50 min	3–5 h
Glulisine	20–30 min	30–90 min	3–4 h
Short-acting			
Regular	30 min–1 h	2–5 h	5–8 h
Intermediate-acting			
NPH	2–4 h	4–12 h	12–18 h
Long-acting			
Glargine	1–1.5 h	No peak	20–24 h
Detemir	1–2 h	No peak	14–24 h

Although no insulin injection regimen satisfactorily mimics normal physiology, premixed insulins are not recommended for pediatric use. When the option is to use regular and NPH insulins, the recommendation should be to provide them as separate insulins, not premixed. Delivering prandial insulin before each meal is superior to postprandial injection and should be preferred if possible [46].

Insulin pumps have become increasingly available to patients with diabetes, and experts highlight their use as the chosen treatment option for many people across all age groups with type 1 diabetes. In adolescents, continuous use of subcutaneous insulin infusion was associated with lower rates of retinopathy (OR, 0.66; 95% CI, 0.045–0.95) and peripheral nerve abnormality (OR, 0.63; 95% CI, 0.42–0.95), suggesting an apparent benefit of continuous subcutaneous insulin infusion over multiple daily injections independent of glycemic control [48]. Insulin pump therapy can assist with reducing episodes of hypoglycemia and is appropriate for youth with diabetes regardless of age. Automated insulin delivery (closed loop) systems improve time in range, including minimizing hypoglycemia and hyperglycemia. Low-glucose suspend systems reduce the severity and duration of hypoglycemia while not leading to deterioration of glycemic control, as measured by HbA1c level. Predictive low-glucose suspend systems can prevent episodes of hypoglycemia and have been shown to be useful for reducing hypoglycemic exposure [44].

Nutritional Management

Nutritional management is one of the fundamental elements of care and education in type 1 diabetes and should be provided at diagnosis and reviewed at least annually by a specialist pediatric diabetes dietitian to increase dietary knowledge and adherence [49]. This management should focus on interventions to ensure normal growth and development, promote lifelong healthy eating habits, optimize glycemic control, prevent associated complications, and avoid overweight and underweight [39, 50]. To establish a nutritional program, health-care providers should consider an individual's energy needs and insulin regimen. In addition, nutritional management and education should be individualized, considering family habits, food preferences, religious or cultural needs, schedules, physical activity, and the patient's and family's abilities in numeracy, literacy, and self-management. The best approach to healthful eating is within the context of the family, focusing on healthy eating for all members [39, 50].

Healthy eating principles targeting an increased consumption of vegetables, fruits, legumes, whole grains, and dairy products are important, with an emphasis on foods with higher fiber contents and lower glycemic loads [50]. Decreased saturated fat intake underlies education; thus, the aim of improving diabetes outcomes and reducing cardiovascular risk is achieved [49, 51]. Recent studies have shown that meals with protein, fat, and more complex carbohydrates delay glucose level increases [52, 53]. Therefore, patients should be taught about all components of food intake and their respective contributions to the daily intake of calories [39, 50].

Matching insulin to the carbohydrate intake in patients receiving intensive insulin therapy requires comprehensive education in carbohydrate counting or experience-based estimation. Regular dietetic assessments by a specialist pediatric diabetes dietitian are necessary to adapt nutritional advice to growth, diabetes management, and lifestyle changes and to permit the identification and treatment of disordered eating patterns [49].

Patients with type 1 diabetes require specialized dietetic support, especially when eating disorders and celiac disease occur, which are more common in type 1 diabetes mellitus [49, 51].

Key dietary behaviors have been associated with improved glycemic outcomes such as the following [49]:

- adherence to an individualized meal plan, particularly carbohydrate intake recommendations;
- avoidance of frequent snacking episodes or large snacks without adequate insulin coverage;
- intake of regular meals and avoidance of skipping meals; and
- avoidance of overtreatment of hypoglycemia and insulin boluses before meals.

At diagnosis, appetite and energy intake are often high to compensate for catabolic weight loss; however, energy intake should be reduced when appropriate weight is restored to prevent overweight or obesity. Energy intake should be sufficient to achieve optimal growth and maintain an ideal body weight [49, 51].

In general, the nutritional recommendations for child and adolescent diabetics are the same as those for children and adolescents without diabetes. No single ideal dietary distribution of calories among carbohydrates, fats, and proteins has been established for people with diabetes, including children; therefore, macronutrient distribution should be individualized while keeping total calorie and metabolic goals in mind [50].

A guide to the distribution of macronutrients that reflects guidelines for healthy eating among children without diabetes could be used when individualizing the dietary management, distributed as follows [49, 51]:

- Carbohydrate, 45–65%
  - Moderate sucrose intake (up to 10% of the total energy intake)
- Fat, 30–35%
  - <10% saturated fat + trans-fatty acids; ≤7% when hyperlipidemia management is required
  - <10% polyunsaturated fat
  - >10% monounsaturated fat (up to 20% of total energy)
- Protein 15–20% (up to 25% in overweight or obese adolescents)

Carbohydrate intake should not be restricted, as it is essential for growth, and as internationally agreed, an excessive restriction of carbohydrates may result in deleterious effects on growth, a higher cardiovascular risk metabolic profile, and increased risk of disordered eating behaviors, as it also may increase the risk of hypoglycemia or potentially impair the effect of glucagon in hypoglycemia treatment. The mean requirement for carbohydrate if a child is consuming 45% energy from carbohydrates is up to 170 g at the age of 10 years and approximately 213 g in adolescents aged 14 years. However, high-quality carbohydrates are important. With a lower carbohydrate intake, children tend to consume more saturated fat. Carbohydrate intake should come predominantly from whole-grain breads and cereals, legumes, fruits, vegetables, and low-fat dairy foods (except for children aged <2 years), preferring those over other sources, especially those containing added sugars [50, 54].

Children and adolescents with type 1 diabetes require education regarding the amount, type, and distribution of carbohydrates over the day. Day-to-day consistency in carbohydrate intake using serving sizes or 15-g carbohydrate exchanges is encouraged for those receiving fixed mealtime insulin doses. A more flexible carbohydrate intake can be achieved using the insulin-to-carbohydrate ratio for children receiving intensive insulin therapy [49, 51].

Carbohydrate counting is a key nutritional intervention for patients with an intensive insulin regimen focused on carbohydrate as the primary nutrient affecting postprandial glycemic response. It aims to improve glycemic control, allows flexibility of food choices, and enables adjustment of the prandial insulin dose according to carbohydrate consumption. The commonly used methods of quantifying carbohydrate include the following: (1) gram increments of carbohydrate, (2) 10- to 12-g carbohydrate portions, and (3) 15-g carbohydrate exchanges. Research has not yet demonstrated a superior method of teaching carbohydrate counting [49].

Nutrition education begins with carbohydrate counting, where consistency rather than accuracy results in optimal glycemic outcomes. Over- or under-calculation by up to 10 g and 15% of the carbohydrate amount is unlikely to yield substantial hypoglycemia and hyperglycemia, respectively [50].

These programs should also consider the glycemic index of foods, which is a ranking of foods based on their acute glycemic impacts. The use of the glycemic index has been shown to provide additional benefit to glycemic control over that observed when only the amount of carbohydrates is considered. Low-glycemic-index foods decrease postprandial glucose excursion compared with carbohydrates with higher glycemic index values [50, 54].

As mentioned earlier, fat and protein are becoming increasingly recognized to also contribute to postprandial hyperglycemia. Both have been found to further delay the increase in postprandial glucose level. Consideration of the impact of fat and protein on glucose levels involves the application of advanced nutritional concepts that are best taught after basic carbohydrate counting skills have been established [54].

The primary goal regarding dietary fat intake in clinical practice is usually to decrease the intakes of saturated fat and trans-fatty acids. Saturated fat is the principal dietary determinant of plasma low-density lipoprotein (LDL) cholesterol. These types of fats are found in full-fat dairy products, fatty meats, and high-fat snacks, which should be avoided. Trans-fatty acids are formed when vegetable oils are processed and solidified. They are found in margarines, deep-frying fat, cooking fat, and manufactured products. Conversely, monounsaturated fatty acids and polyunsaturated fatty acids, which are found in vegetable oils, nuts, nut butters, and oily fish, can be used as substitutes to improve the lipid profile [54].

Recommendations for decreasing protein intake during childhood range from approximately 2 g/kg/day in early infancy to 1 g/kg/day for 10-year-olds and to 0.8–0.9 g/kg/day in later adolescence. Protein intake promotes growth only when sufficient total energy is available. High-protein diets (>25% total energy) are not generally advised for children with type 1 diabetes, as they may impact growth and vitamin and mineral intakes, except for obese adolescents. Inclusion of sources of vegetable proteins, such as legumes, in diets should be encouraged, as well as that of sources of animal protein, such as fish, lean cuts of meat, and low-fat dairy products [51, 55].

Children with type 1 diabetes have the same vitamin and mineral requirements as healthy children [51], so their intake should be as recommended in nutritional guidelines for the general pediatric population [56]. No clear evidence of the benefit from vitamin or mineral supplementation has been found in children diagnosed with type 1 diabetes who do not have underlying deficiencies [51].

High dietary sodium intake in children with type 1 diabetes is common and relates to vascular dysfunction. Sodium intake should be limited to at least that recommended for the general population. The guidelines for sodium intake in children 1–3 years are as follows: 1000 mg/day (2.5 g salt/day); 4–8 years, 1200 mg/day (3 g salt/day); and 9 years and older, 1500 mg/day (3.8 g salt/day) [54].

Antioxidants are strongly recommended for cardiovascular protection in young people with type 1 diabetes. Many fresh fruits and vegetables are naturally rich in antioxidants (tocopherols, carotenoids, vitamin C, and flavonoids), so their intake should be encouraged [51].

Estimates of dietary fiber intakes in children in many countries are lower than those recommended (3.3 g of fiber per megajoule or 14 g/1000 kcal in children aged >1 year). Intake of a variety of fiber-containing foods such as legumes, vegetables, fruits, and whole-grain cereals should be encouraged, as it promotes healthy bowel function, helps reduce lipid levels, and may be useful for enhancing protection against cardiovascular disease. Fiber-containing foods may also help improve satiety and replace more energy-dense foods. Processed foods tend to be lower in fiber; hence, unprocessed fresh foods should be encouraged. Fiber in the diet should be increased slowly to prevent abdominal discomfort, and any increase in fiber intake should be accompanied by an increase in fluid intake [49].

The dietary recommendations for specific insulin regimes include the following [54]:

Twice daily insulin regimens: Day-to-day consistency in carbohydrate intake to balance the insulin action profile and prevent hypoglycemia during periods of peak insulin action. The carbohydrate content consumed in the meals eaten at the time of insulin doses can be flexible if the patient or the family is taught to adjust the short/rapid-acting insulin to the carbohydrate eaten. Most of the time, this type of regimen requires carbohydrate intake before bed to help prevent nocturnal hypoglycemia.

- Intensive insulin regimens: individualized insulin-to-carbohydrate ratios should be used, as they enable the pre-prandial insulin dose to be matched to the carbohydrate intake. Snacks without meal boluses should be avoided, as it results in deterioration in glycemic control.

Exercise Management in Type 1 Diabetes

Regular exercise is important because it promotes and improves health and well-being, physical fitness, strength building, weight management, social interaction, self-esteem building, and creation of healthful habits for adulthood, and can help patients achieve their target lipid profile, body composition, fitness, and glycemic goals. However, barriers to exercise include fear of hypoglycemia and hyperglycemia, loss of glycemic control, and inadequate knowledge around exercise management [57].

Children and adolescents with diabetes have the same physical activity requirements as their peers without diabetes. The physical activity targets for toddlers (1–2 years)

and preschoolers (3–4 years) are a minimum of 180 min of physical activity of any intensity throughout the day with an emphasis on movement-developing skills and varied activities throughout the day. Preschool physical activity should progress toward at least 60 min of energetic play near the age of 5 years. The recommendations for children (5–11 years) and youths (12–17 years) are a minimum of 60 min of moderate- to vigorous-intensity physical activity daily to achieve health benefits (at least 420 min/week of exercise); vigorous-intensity aerobic activities at least 3 days/week, with ≤2 consecutive days between aerobic activities; and muscle- and bone-strengthening activities (resistance training) at least 3 days/week in the absence of contraindications [58–60].

Overall, youths with type 1 diabetes are recommended to participate in ≥60 min of daily physical activity, including resistance and flexibility training. Although comorbid conditions or diabetes complications are uncommon in the pediatric population, patients should be medically evaluated for these conditions, which may restrict participation in an exercise program [50].

Sedentary time should also be minimized to achieve health benefits. Recreational screen time (television, computer, and video games) is not recommended for infants and toddlers, should be limited to <1 h/day for preschoolers, and should not exceed 2 h/day for older children. Patients should also minimize the time spent indoors, prolonged sitting, and sedentary transport [61].

To avoid hypoglycemia, patients should take the following precautions [57]:

- Decrease the prandial insulin level for the meal/snack before exercise and/or increasing food intake. Patients on insulin pumps can lower basal rates by approximately 10 to ≥50% or suspend the increase in basal rates for 1–2 h during exercise.
- Decreasing basal rates or long-acting insulin doses by approximately 20% after exercise may reduce delayed exercise-induced hypoglycemia.
- If patients are unable to lower their insulin levels through exercise, they should consider increasing their carbohydrate intake at a rate of approximately 0.5 g/kg/h of activity.
- If patients are able to lower their insulin levels, they should consider the timing of exercise relative to their last meal.
  - If activity occurs ≤3 h after a meal, they should consider bolus insulin reduction. In case of <60 min duration, the reduction will depend on the exercise intensity as follows: light, 25%; moderate, 50%; or heavy, 75%. In case of ≥60 min duration, they should consider a 50% reduction in light-intensity exercise and 75% reduction in moderate/heavy-intensity exercise.
  - If activity occurs >3 h after a meal, patients must consider basal insulin reduction. Patients with multiple-dose insulin should consider a 20% reduction in basal insulin on days with prolonged activity. Patients with continuous subcutaneous insulin infusion may reduce their basal insulin levels by 50–90% in the 60–90 min before the start of exercise until the exercise ends or even consider pump suspension at the start of exercise.
- Aerobic exercise may require an initial carbohydrate intake (15–20 g). The response to a downward trend in glucose during exercise should be the ingestion of 8–20 g of rapidly acting carbohydrate.
- Consider an overnight basal rate reduction of 10–40% on evenings after prolonged aerobic exercise or resistance training.

Blood glucose targets prior to exercise should be 90–250 mg/dL (5.0–13.9 mmol/L). Additional carbohydrate intake during and/or after exercise should be considered, depending on the duration and intensity of physical activity, to prevent hypoglycemia. Prior to exercise (1–3 h), a low-fat, 1- to 1.5-g/kg carbohydrate containing meal should be consumed to maximize glycogen stores and the availability of carbohydrate for exercise without prior insulin adjustment. If the patient has a blood glucose level of <5 mmol/L, engages in low- to moderate-intensity aerobic activities, and is fasting, 10–15 g of carbohydrate may prevent hypoglycemia. After exercise, carbohydrate intake must be sufficient to ensure replacement of both muscle and hepatic glycogen stores and prevent post-exercise hypoglycemia. Consuming as high as 1.5 g/kg of carbohydrate mixed with protein and low-fat snack after training ensures muscle recovery, requiring carefully adjusted insulin doses. Exercise lasting ≥60 min may require additional carbohydrate to maintain performance [50, 54].

Effect of Treatment on the Honeymoon Period of Type 1 Diabetes

A beneficial effect of intensive early insulin therapy on the protection of pancreatic beta cell function in newly diagnosed type 1 diabetes mellitus has been demonstrated [62, 63]. This protective effect results in better glycemic control and fewer complications [62, 64]. Early small doses of insulin have been observed to be effective to prevent beta cell failure in slowly progressive type 1 diabetes and have been recommended for patients with positive antibodies [65, 66]. During the honeymoon phase, the insulin requirement decreases, and basal insulin doses of 0.2–0.6 units/g/day during this phase may preserve beta cell function [41].

Immunomodulatory agents have been used to preserve beta cell function, with promising results reported for anti-CD3, Diapep277, oral insulin, and GAD65 treatments. The possibility of beta cell function (high residual C-peptide secretion) preservation in individuals within the first months of diagnosis has been shown in clinical trials with these immunomodulators [63, 64, 66, 67].

Glucagon

Intensive insulin treatment in type 1 diabetes reduces the incidence of complications but has an increased risk of hypoglycemia and weight gain. The main goal of type 1 diabetes treatment has been the simulation of physiological insulin secretion in healthy people. However, type 1 diabetes is a dual-hormone disease, for which the combination of insulin and glucagon might be more appropriate. Glucagon substitution in response to hypoglycemia as an alternative to carbohydrate consumption could potentially reduce the risk of weight gain. Closed-loop dual-hormone treatment could potentially benefit the treatment of type 1 diabetes. Until now, the use of glucagon has been limited by the need for reconstitution immediately before use. However, it can be expected that stable compounds available for dual-hormone treatment in the future will improve metabolic control for patients with type 1 diabetes [68, 69].

Islet Transplantations and Stem Cell Therapy

The only possible cure for patients with type 1 diabetes is the possibility of replacement pancreatic beta cells. Hence, transplantation strategies have gained much interest. Research into the replacement of beta cells has had significant advances in islet isolation, engraftment, and immunosuppressive strategies. However, the main remaining limitations are the insufficient supply of human tissue and the need for lifelong immunosuppression therapy [70, 71]. In an effort to find sources of insulin-producing beta cells, alternatives such as nonhuman donor cells (mainly porcine beta cells) or the possibility of deriving pluripotent stem cells from somatic cells have been encouraged. Cell reprogramming and differentiation to obtain patient-specific beta cells have allowed the possibility of cell therapy without immunosuppression [71].

Addition of Metformin for Children with Type 1 Diabetes Mellitus

Frequently, the metabolic control of patients with type 1 diabetes mellitus worsens during adolescence secondary to increases in weight and insulin resistance as a result of puberty hormones. Therefore, the use of metformin to improve insulin sensitivity in this group of patients has been considered. In a recent meta-analysis (6 clinical trials, $n = 325$), the addition of metformin in the treatment of pediatric patients with type 1 diabetes resulted in a modest decrease in total insulin daily dose (mean difference, −0.15 unit/kg/day; 95% CI, −0.24 to 0.06) and body mass index (mean difference, −1.46; 95% CI, −2.54 to 0.38). In addition, metformin was not superior to placebo in other metabolic control variables such as HbA1c level, lipid profile, and ketoacidosis events. The authors noted that the current evidence does not support the use of metformin in type 1 diabetes mellitus in pediatric patients to improve HbA1c. Future studies are needed to evaluate the long-term durability of the reductions in total insulin daily dose and body mass index achieved by adding metformin to insulin [72].

Management of Hypoglycemia in Children and Adolescents with Diabetes

Hypoglycemia is the most common acute complication of type 1 diabetes and is the major barrier to achieving optimal glycemic control [40, 73].

Hypoglycemia is defined as a decrease in the blood glucose level that exposes the patient to potential harm. Blood glucose levels <65 mg/dL have been often accepted as the cutoff level for defining hypoglycemia. However, a threshold of 70 mg/dL is used to start treatment because of the possibility of further decreases [40, 74].

Hypoglycemia is also classified as symptomatic or asymptomatic. The signs and symptoms in children are as follows [40, 75]:

- **Autonomic:** shakiness, sweatiness, trembling, palpitations, and pallor
- **Neuroglycopenic:** poor concentration, blurred or double vision, disturbed color vision, difficulty hearing, slurred speech, poor judgment and confusion, problems with short-term memory, dizziness and unsteady gait, loss of consciousness, seizure, and death
- **Behavioral:** irritability, erratic behavior, agitation, nightmares, and inconsolable crying
- **Nonspecific symptoms:** hunger, headache, nausea, and tiredness

Symptoms of hypoglycemia may occur at higher glucose levels in children compared with adults, and the thresholds may be altered by chronic hypoglycemia. Children have a higher risk of severe hypoglycemia than adults. In this age group, severe hypoglycemia is most often defined as an event associated with seizure or loss of consciousness [40].

Milder hypoglycemia should be treated with 10–15 g of oral glucose (approximately 0.3 g/kg) to increase blood glucose to approximately 54–70 mg/dL. This can be achieved by glucose tablets or sweetened fluids such as juice. After initial treatment, blood glucose should be retested in 10–15 min. In case of an inadequate response, treatment should be repeated, and the blood glucose level must be retested in another 10–15 min to confirm that a glucose level of 100 mg/dL has been reached. In some circumstances, this should be followed by additional complex carbohydrates (fruit, bread, cereal, or milk) to prevent the recurrence of hypoglycemia [40].

However, if the child is semiconscious/unconscious, sugar or any other powdery substance or thin liquids such as a glucose solution or honey should not be given forcibly to the child. The child should be put in a lateral position to prevent aspiration, and a thick paste of glucose (glucose powder with a few drops of water or table sugar crushed into powdered sugar with the consistency of thick cake icing) should be smeared inside the cheek; the efficacy of this practice is anecdotal [33].

Severe hypoglycemia requires urgent treatment. In a hospital setting, patients should be treated with intravenous glucose. The recommended dose is 10–30%, for a total of 200–500 mg/kg of glucose (10% glucose, 2–3 mL/kg). Rapid administration or excessive concentration (i.e., glucose 50%) may result in an excessive rate of osmotic change and risk of cerebral edema [40].

In settings outside the hospital, intramuscular or subcutaneous glucagon should be given (<12 years: 0.5 mg, >12 years: 1.0 mg or 10–30 μg/kg body weight). Caregivers should always have glucagon available and receive training in using it [40, 75].

Hypoglycemia should be prevented because it is associated with psychosocial dysfunction and, in rare cases, leads to permanent long-term sequelae and may be potentially life-threatening. Diabetes education is critical for preventing hypoglycemia. Patients, parents, and caregivers should be alert to situations in which increased glucose monitoring is required and when treatment regimens need to be changed. They should be alert to recognize the early signs of hypoglycemia, have a glucometer available for confirmation, and provide some source of glucose. Sleep is a time of particular risk for severe hypoglycemia, and asymptomatic hypoglycemia is common; for this reason, glucose levels are recommended to be monitored overnight, particularly in the presence of an additional risk factor that may predispose to nocturnal hypoglycemia. Currently available technologies such as continuous glucose monitoring and automated insulin suspensions have reduced the duration of hypoglycemia [75].

Children and adolescents with type 1 diabetes should wear some form of identification to alert others of their diabetes. If unexplained hypoglycemia occurs frequently, evaluation for unrecognized celiac and Addison's disease should be considered [40].

Sickness

Children and adolescents whose diabetes is under good metabolic control should not experience more illness or infections than children without diabetes. However, when any illness occurs, someone with diabetes potentially experiences hyperglycemia, hyperglycemia with ketosis, hyperglycemia with ketoacidosis, or hypoglycemia, and requires education and treatment to prevent exacerbation or even possible death [76, 77].

Many illnesses are associated with higher levels of stress hormones, which promote gluconeogenesis and insulin resistance. Severe illness increases ketone body production because of the inadequate provision of insulin under such circumstances and thus can contribute to acidosis, nausea, and vomiting, worsening dehydration and ultimately compromising the acid-base balance, resulting in metabolic decompensation, ketoacidosis, coma, and death. Illnesses associated with vomiting and diarrhea, such as gastroenteritis, often lower blood glucose levels rather than cause hyperglycemia while simultaneously producing a type of starvation ketosis, which exacerbates the situation [76].

Education about the effects of sick days is a critical component of diabetes management at home. The general sick-day diabetes management principles include the following [76, 77]:

- More frequent blood glucose and ketone (urine or blood) monitoring, at least every 3–4 h and sometimes every 1–2 h, including throughout the night.
- During sick days, do not stop insulin, even in the fasting state.
- During sick days, the insulin dose may need to be temporarily increased or decreased.
- When vomiting occurs, it should always be considered a sign of insulin deficiency until proven otherwise.
- Monitor and maintain salt and water balance.
- Treat the underlying precipitating illness.
- Sick-day guidelines, including insulin adjustment, should be taught soon after diagnosis and reviewed at least annually with patients and family members with a goal of minimizing and/or avoiding diabetic ketoacidosis and similarly minimizing and/or avoiding illness-associated hypoglycemia.

In case of loss of appetite, replacing meals with easily digestible food and sugar-containing fluids provides energy (carbohydrates) and may help prevent further ketosis. Necessary sick-day management supplies at home include glucose tablets, sweets, or candies, as well as dried fruit to prevent hypoglycemia; clean cool water to provide hydration and prepare salty soups; sugar- and electrolyte-containing fluids such as sports drinks or electrolyte mixtures to provide hydration,

glucose, and salts; and easy-to-digest carbohydrates such as crackers or rice [76, 77].

Additional doses of short/rapid-acting insulin are required, with careful monitoring to reduce blood glucose levels, prevent ketoacidosis, and avoid hospital admission. The dose and frequency of injection will depend on the level and duration of hyperglycemia and the severity of ketosis (Table 64.3). Such supplemental doses are usually given subcutaneously but may also be given intramuscularly with health-care professional advice.

In the case of a patient who is a pump user, the previously mentioned key points of sick-day management are the same as those for a patient on insulin injections; however, specific management is recommended as follows [77]:

Hyperglycemia with negative ketones

- Give a correction bolus using a pump, and perform a blood glucose test hourly.
- Drink low-carbohydrate fluids or salty liquids.
- If the blood glucose level is decreased after 1 h, recheck again in 1–2 h to decide whether another bolus is needed.
- If the blood glucose level has not decreased, then give a bolus by syringe or pen.

Hyperglycemia with blood ketone levels >0.6 mmol/L or positive urine ketones

- Give a sick-day bolus by injection with pen or syringe using the guidelines in Table 64.3.
- Change the catheter, and check to be sure the pump is working.
- Reestablish insulin infusion with a new insulin infusion set and a cannula, with a temporary basal rate increase of 120–150%.
- Monitor blood glucose levels hourly, and recheck ketone levels at least every 4 h.
- Drink extra high-carbohydrate fluids if ketone levels are elevated and the blood glucose level is low or low-carbohydrate fluids if the blood glucose is elevated with or without elevated ketone levels.
- If the blood glucose level remains high; ketones persist; nausea, vomiting, or abdominal pain develops; or confusion or problems of staying awake and alert develop, proceed to the hospital for assessment.

If hypoglycemia (<65–70 mg/dL) and nausea or food refusal persists, a "mini glucagon treatment" (if available) may reverse the hypoglycemia and enable oral fluid intake. The recommended doses are as follows [77]:

Table 64.3 Fast-acting insulin dose calculation on sick days (adapted from Brink et al. [77])

Ketones		Blood glucose				
Blood (mmol/L)	Urine ketones	<100 mg/dL	100–180 mg/dL	180–250 mg/dL	250–400 mg/dL	400 mg/dL
<0.6	Negative or trace	Do not give extra insulin	No need to worry	Increase the insulin dose in the next meal if the blood glucose level is still elevated	Give extra 5% of the total daily dose or 0.05 U/kg	Give extra 10% of the total daily dose or 0.1 U/kg. Repeat if needed
0.6–0.9	Trace or small	Extra carbohydrates and fluids are needed	Extra carbohydrates and fluids are needed	Give extra 5% of the total daily dose or 0.05 U/kg	Give extra 5–10% of the total daily dose or 0.05–0.1 U/kg	Give extra 10% of the total daily dose or 0.1 U/kg. Repeat if needed
1.0–1.4	Small or moderate	Extra carbohydrates and fluids are needed	Extra carbohydrates and fluids are needed. Give an ordinary bolus dose	Extra carbohydrates and fluids are needed. Give 5–10% of the total daily dose or 0.05–0.1 U/kg	Give extra 5–10% of the total daily dose or 0.05–0.1 U/kg	Give extra 10% of the total daily dose or 0.1 U/kg. Repeat if needed
1.5–2.9	Moderate or high	Extra carbohydrates and fluids are needed	Extra carbohydrates and fluids are needed. Give 5% of the total daily dose or 0.05 U/kg. Repeat when the blood glucose level has increased	Extra carbohydrates and fluids are needed. Give 10% of the total daily dose or 0.1 U/kg	Give extra 10–20% of the total daily dose or 0.1 U/kg. Repeat the dose after 2 h if the ketone levels do not decrease	Consider evaluation at the emergency department
>3.0	High	Extra carbohydrates and fluids are needed. May need IV glucose if the child cannot eat or drink	Extra carbohydrates and fluids are needed. Give 5% of the total daily dose or 0.05 U/kg. Repeat when the blood glucose level has increased	Extra carbohydrates and fluids are needed. Give 10% of the total daily dose or 0.1 U/kg	Give extra 10–20% of the total daily dose or 0.1 U/kg. Repeat the dose after 2 h if the ketone levels do not decrease	Consider evaluation at the emergency department

- <2 years old = 0.02 mg = 2 units on insulin syringe
- 2–15 years old = 0.01 mg per year of age = 1 unit on insulin syringe per year of age
- >15 years old = 0.15 mg = 15 units on insulin syringe

Diabetes may also be an important risk factor for increased severity of illness and mortality in COVID-19 infections. An association between COVID-19 and new-onset type 1 diabetes and severe metabolic complications of preexisting diabetes, including DKA and hyperosmolarity, for which exceptionally high doses of insulin have been needed, has been reported. In the context of the COVID-19 pandemic, telephone consultations for sick-day management and routine diabetes care should be encouraged. This may help in the identification of children at risk of DKA, prevention of DKA, and avoiding urgent hospital visits. Families should be educated to not omit insulin, maintain hydration, treat the underlying symptoms of an intercurrent illness, and follow the general advice regarding healthy eating and continuing physical activity at home [78].

Surgery

When children with diabetes require surgery or other procedures requiring sedation or anesthesia, optimal management should maintain adequate hydration and near-normal glycemia while minimizing the risk of hypoglycemia [76]. The safe management of patients with type 1 diabetes in the perioperative period requires a consideration of each child's specific treatment, glycemic control, intended surgery, and anticipated postoperative course [79].

The presurgical assessment should be performed several days before surgery to allow an assessment of glycemic control, electrolyte status, and ketone levels. If glycemic control is known to be poor and surgery is not urgent, the procedure should be delayed until glycemic control has improved. If surgery cannot be delayed, admission to the hospital before surgery should be considered for stabilization of glycemic control [79].

Intravenous access, infusion of glucose, and frequent blood glucose monitoring are essential whenever general anesthesia is given. Glucose 5% is usually sufficient, but glucose 10% may be necessary when the risk of hypoglycemia is high. To minimize the risk of hypoglycemia, children should receive a glucose infusion when fasting for >2 h before general anesthesia [76, 79, 80].

The glucose target during surgical procedures is 90–180 mg/dL [79]. The appropriate glycemic targets during the perioperative period remain controversial and are less clear than that for surgery or postoperative control. However, studies in adults have not demonstrated any adverse effects of maintaining perioperative glycemic levels between 90 and 200 mg/dL [76, 80].

The stress from surgery leads to a complex neuroendocrine stress response characterized by hyperglycemia and a catabolic state [80]. In addition, hyperglycemia has been associated with an increased risk of postoperative infection, so it must be avoided. To achieve optimal glycemic control, the insulin dosage may need to be increased on the day of a major surgery and for approximately 2 days after surgery. This is best achieved by continuous IV insulin infusion even after the resumption of oral feeding [76, 80].

Before emergency surgery, the blood glucose, blood ß-hydroxybutyrate (if available), or urinary ketone concentration, serum electrolyte levels, and blood gases should always be checked if ketone or blood glucose levels are high. If ketoacidosis is present, the established treatment protocol for diabetic ketoacidosis should be followed and surgery should be delayed, if possible, until circulating volume and electrolyte deficits are corrected. If no ketoacidosis is observed, IV fluids and insulin management are started for elective surgery [79, 80].

Pediatric patients with type 1 diabetes need insulin, even while fasting, to avoid ketoacidosis and require careful blood glucose monitoring (hourly) before the procedure to detect hypoglycemia and hyperglycemia. At least 2 h before surgery, an IV insulin infusion (dilute 50 units regular [soluble] insulin in 50 mL of normal saline; 1 unit = 1 mL) and administration of glucose 5% (10% if increased risk of hypoglycemia is a concern) are started. If the blood glucose level is high (>250 mg/dL), 0.45 or 0.9% NaCl without glucose is used and the insulin supply is increased, but 5% dextrose should be added if the blood glucose level decreases to <250 mg/dL. Infusion is started at the following blood glucose levels: 0.025 mL/kg/h for <100–140 mg/dL, 0.05 mL/kg/h for 141–215 mg/dL, 0.075 mL/kg/h for 220–270 mg/dL, and 0.1 U/kg/h for >270 mg/dL [76, 79].

Blood glucose level should be monitored every 30–60 min during the operation and until the child recovers from anesthesia. The dextrose infusion and insulin must be adjusted to maintain the blood glucose levels within 90–180 mg/dL. Insulin infusion is continued if the blood glucose level is <90 mg/dL, as this will cause rebound hyperglycemia; instead, the rate of infusion is reduced. The IV insulin infusion may be stopped temporarily if the blood glucose level is <55 mg/dL, but only for 10–15 min [33, 76, 80].

Patients may initially receive an intravenous (IV) infusion without dextrose for minor surgeries or procedures lasting for <2 h if treated with basal/bolus insulin regimen or continuous subcutaneous insulin infusion. They should initially receive an IV infusion with dextrose for major surgeries or procedures (lasting for at least 2 h) or if treated with NPH insulin [80].

Once the child is able to resume oral nutrition, the child's usual diabetes treatment regimen should be continued. Short- or rapid-acting insulin (based on the child's usual insulin:

carbohydrate ratio and correction factor) should be administered, if needed, to reduce hyperglycemia or to match the food intake [79, 80].

Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

Diabetic ketoacidosis results from a deficiency of circulating insulin and increased levels of counter-regulatory hormones. Several risk factors lead to diabetic ketoacidosis in newly diagnosed cases, such as younger patients (<2 years), delayed diagnosis, lower socioeconomic status, and countries with low prevalence rates of type 1 diabetes. In the case of patients with a known diagnosis, the risk factors include insulin omission, poor metabolic control, previous episodes of diabetic ketoacidosis, gastroenteritis with persistent vomiting, inability to maintain hydration, psychiatric and eating disorders, challenging social and family circumstances, peripubertal and adolescent girls, limited access to medical services, and failures of insulin pump therapy [81].

The combination of absolute or relative insulin deficiency and high counter-regulatory hormone concentrations results in an accelerated catabolic state with increased glucose production, resulting in hyperglycemia and hyperosmolality; it also increases lipolysis and ketogenesis and causes ketonemia and metabolic acidosis. If this cycle is not interrupted by exogenous insulin and fluid and electrolyte therapies, fatal dehydration and metabolic acidosis will ensue [81].

The clinical signs of diabetic ketoacidosis include the following: dehydration, tachycardia, tachypnea, deep respiration (Kussmaul respiration), ketone smell on the breath (odor of nail polish remover or rotten fruit), nausea, vomiting, abdominal pain (which may mimic an acute abdominal condition), confusion, drowsiness, progressive reduction in the level of consciousness, and eventually, loss of consciousness [81].

The biochemical criteria for the diagnosis of diabetic ketoacidosis are as follows [81]:

- Hyperglycemia (blood glucose level >200 mg/dL)
- Venous pH < 7.3 or bicarbonate level <15 mmol/L
- Ketonemia and ketonuria

The criteria for hyperglycemic hyperosmolar state (HHS) include the following [81]:

- Plasma glucose concentration >600 mg/dL
- Venous pH > 7.25; arterial pH > 7.30
- Serum bicarbonate level >15 mmol/L
- Low ketonuria and absent-to-mild ketonemia
- Effective serum osmolality >320 mOsm/kg
- Altered consciousness (e.g., obtundation and combativeness) or seizures

Emergency assessment should follow the general guidelines for Pediatric Advanced Life Support and include the following: immediate measurement of blood glucose level, blood or urine ketone levels, serum electrolyte levels, blood gases, and full blood count, and assessment of the severity of dehydration and level of consciousness [81].

The goals of therapy are to correct dehydration, correct acidosis, and reverse ketosis; slowly correct hyperosmolality and restore blood glucose to near-normal; monitor for complications of diabetic ketoacidosis and its treatment; and identify and treat any precipitating event. Management should be conducted in centers that are experienced in the treatment of diabetic ketoacidosis in children and adolescents and where vital signs, neurological status, and laboratory results can be monitored frequently [81].

Fluid replacement should begin before starting insulin therapy. Expand the volume, as required, to restore peripheral circulation. For patients who are severely volume depleted but not in shock, volume expansion should begin with 0.9% saline with 10- to 20-mL/kg doses over 1–2 h and may need to be repeated until tissue perfusion is adequate. In patients with diabetic ketoacidosis in shock, circulatory volume with isotonic saline in 20-mL/kg boluses should be infused as quickly as possible [82].

The subsequent rate of fluid administration, including the provision of maintenance fluid requirements, to replace the estimated fluid deficit evenly over 48 h should be calculated. Subsequent fluid management should include an isotonic solution for at least 4–6 h. Deficit replacement after 4–6 h should be with a solution with a tonicity of ≥0.45% saline with added potassium [82].

Insulin therapy should begin with 0.05–0.1 U/kg/h at least 1 h after starting fluid replacement therapy. In HHS, insulin administration should begin at a dose of 0.025–0.05 U/kg/h once plasma glucose is no longer declining at a rate of at least 3 mmol/L (50 mg/dL) per hour with fluid alone [81, 82].

During volume expansion and after commencing insulin therapy, the plasma glucose concentration typically decreases. To prevent a rapid decrease and hypoglycemia, 5% glucose should be added to the IV fluid when the plasma glucose level decreases to approximately 250–300 mg/dL or sooner if the rate of decrease is precipitous. Dextrose at 10% or even 12.5% may be needed to prevent hypoglycemia while continuing the insulin infusion to correct metabolic acidosis [81].

If the patient is hyperkalemic, potassium replacement therapy is deferred until the urine output is documented. Otherwise, 40-mmol potassium/L is started in the infusion or 20-mmol potassium/L in a patient receiving fluid at a rate of >10 mL/kg/h [81].

Bicarbonate administration is not recommended, except for the treatment of life-threatening hyperkalemia. The warn-

ing signs and symptoms of cerebral edema, including headache and slowing of heart rate, a change in neurological status (restlessness, irritability, increased drowsiness, or incontinence), specific neurological signs, increasing blood pressure, and decreased oxygen saturation, should be monitored. In patients with multiple risk factors of cerebral edema, mannitol or hypertonic saline should be available at bedside, and the dose to be given should be calculated beforehand. If the patient's neurological status deteriorates acutely, hyperosmolar therapy should be given immediately [81].

Management of an episode of DKA is not complete until an attempt has been made to identify and treat the cause so that it could be prevented. Recurrent DKA without a preceding febrile or vomiting illness is almost always the result of psychosocial problems and failure to take insulin [81].

In cases with uncomplicated mild to moderate ketoacidosis, subcutaneous rapid-acting insulin analogs are effective and can be used if IV insulin is not feasible. Subcutaneous regular insulin is also an alternative if rapid-acting insulin analogs and IV regular insulin infusion are not available. The suggested starting dose is 0.15 U/kg every 2–4 h. Subcutaneous insulin therapy may not be appropriate in youths with severe dehydration or young children (aged <2 years) [78].

Autoimmune Conditions

Patients with type 1 diabetes have an increased frequency of other autoimmune diseases. Autoimmune thyroid disease is the most common (17–30%). At the time of diagnosis, approximately 25% of patients have thyroid autoantibodies, and their presence is predictive of thyroid dysfunction (most commonly hypothyroidism). Thyroid dysfunction can alter glycemic control and linear growth rate. Therefore, thyroid function tests should be performed soon after a period of metabolic stability. Testing for anti-thyroid peroxidase and anti-thyroglobulin antibodies and measurement of thyroid-stimulating hormone concentrations soon after diagnosis are recommended. If the values are normal, rechecking should be performed every 1–2 years or sooner if the patient presents symptoms of thyroid dysfunction, goiter, abnormal growth rate, or unexplained glycemic variation [2, 83]. Hyperthyroidism is less common than hypothyroidism in association with type 1 diabetes but is still more common than in the general population. Hyperthyroidism may be due to Graves' disease or the hyperthyroid phase of Hashimoto's thyroiditis [83].

Celiac disease occurs in 1.6–16.4% of patients with type 1 diabetes. Screening by measuring serum levels of IgA and anti-tissue transglutaminase antibodies is recommended and should be performed at the time of diabetes diagnosis and at 2 and 5 years thereafter, as it is frequently asymptomatic [83]. In cases of IgA deficiency, IgG tissue transglutaminase antibodies or IgG deamidated gliadin peptide antibodies should be measured. Repeat screening within 2 years of diabetes diagnosis and then again after 5 years is recommended. More frequent screening is recommended for patients with first-degree relatives with celiac disease, growth failure, weight loss, failure to gain weight, gastrointestinal symptoms (diarrhea, flatulence, abdominal pain, or signs of malabsorption), unexplained hypoglycemia, or uncontrolled glycemia. The diagnosis could be confirmed with a small bowel biopsy, and patients should be placed on a gluten-free diet to reduce symptoms and frequency rates of hypoglycemia [2].

Addison's disease is suspected on the basis of the clinical picture of frequent hypoglycemia, unexplained decrease in insulin requirements, increased skin pigmentation, lassitude, weight loss, hyponatremia, and hyperkalemia. The diagnosis is confirmed by the demonstration of low morning cortisol levels in the presence of elevated basal ACTH levels, with an inadequate response to an ACTH stimulation test and positive anti-adrenal (21-hydroxylase) antibodies. Treatment with a glucocorticoid is urgent and lifelong. In some cases, the therapy must be supplemented with a mineralocorticoid such as fludrocortisone [83].

Another rare disorder is autoimmune gastritis, which includes chronic inflammation with destruction of parietal cells of the corpus and fundus of the stomach as a consequence of parietal cell antibodies as the principal immunological marker. Chronic damage to the proton pump may result in hypochlorhydria/achlorhydria, hypergastrinemia, and iron deficiency anemia due to decreased gastric secretion and decreased iron absorption. Parietal cell antibodies may also inhibit intrinsic factor secretion, which leads to vitamin B12 deficiency and pernicious anemia. The prevalence rates of parietal cell antibodies in children with type 1 diabetes range from 5.3 to 7.5%. Physicians should be aware of the possibility of parietal cell antibodies in cases of unclear anemia (microcytic and macrocytic) or gastrointestinal symptoms [83].

Psychosocial Issues

Type 1 diabetes places a substantial behavioral and psychological burden on young people and their families. Approximately one-third of adolescents with type 1 diabetes need mental health support, and their parents are also at increased risk of psychological distress [84]. Youth with diabetes should be assessed for psychosocial and diabetes-related distress, generally starting at 7–8 years. The offering to Adolescents should be offered the opportunity to interact with their care providers strting at the age of 12, or

when developmentally appropriate [2]. Diabetes management in pediatric patients confers challenges that require family teamwork to maintain adherence and glycemic control. During follow-up, health-care providers should be alert to psychosocial issues and stresses that could affect adherence to treatment. Diabetes can impact mental health problems such as distress, fear of hypoglycemia and hyperglycemia, anxiety, disordered eating behaviors, or depression [2, 34]. In case of hospitalization, children with type 1 diabetes have higher odds (3.5) of being discharged from the hospital with a comorbid mood or anxiety disorder than other children [85]. These psychosocial factors are related to nonadherence, poor glycemic control and quality of life, and diabetes complications. Thus, screening for psychosocial distress and mental health problems is important, and referrals to trained mental health professionals as integral members of the pediatric diabetes multidisciplinary team should be provided to ensure optimal clinical care and long-term outcomes for these children [2, 34].

Young people with diabetes, especially those with a background of early diabetes onset, severe hypoglycemia, or chronic hyperglycemia, are at increased risk of mild decrements in general cognitive ability, information processing skills, executive functions, and academic achievement. Therefore, assessment of developmental progress in all domains of functioning (physical, intellectual, academic, emotional, and social development) should be conducted on a routine basis. Children with learning difficulties should be referred for a psycho-educational or neuropsychological evaluation to determine if learning disabilities are present [86].

Routine assessment should be performed with developmental adjustment to and understanding of diabetes management, including diabetes-related knowledge, insulin adjustment skills, goal setting, problem-solving abilities, regimen adherence, and self-management autonomy and competence. This is especially important during late childhood and prior to adolescence, when in many families, the child may take on diabetes management responsibilities without adequate maturity for effective self-management. The interdisciplinary team should provide interventions to emphasize appropriate family involvement and support in diabetes management, effective problem-solving and self-management skills, and realistic expectations about glycemic control [86].

Vaccination

Patients with diabetes mellitus are more susceptible to infections, for which immune system deficiency could be a reason. Routine vaccinations are recommended for children with diabetes, as for the general population, according to age [87]. However, the antibody responses to pertussis, diphtheria, tetanus, mumps, and hepatitis B vaccines are similar between patients with and without diabetes, although the response to measles and rubella vaccinations could be lower [88].

Pregnancy Prevention

Pre-pregnancy counseling is an important tool in chronic endocrine conditions to reduce the risk to mother and fetus. Starting at puberty, preconception counseling should be incorporated for all girls [2]. The management of pregnancies complicated by diabetes mellitus requires coordination among the team of obstetricians, endocrinologists, dietitians, and psychologists. The prevention of unintended pregnancies among teens with diabetes mellitus is critically important because these patients are as likely as healthy teens, in whom 83% pregnancies are unintended, to be sexually involved. Implants and intrauterine devices represent the most effective, safest, and most successful contraceptive options for adolescents [89].

Management of Cardiovascular Risk Factors

Pediatric patients with type 1 diabetes are at higher risk of early adult-onset cardiovascular disease. Adolescents with type 1 diabetes exhibit early changes in blood pressure, peripheral vascular function, and left ventricular myocardial deformation indexes, and detection could benefit from early therapeutic interventions [90].

Hypertension

Blood pressure should be measured at each consultation using an appropriate-size cuff, with the patient seated and relaxed. The result should be compared with normal levels for age, sex, and height. Children with high normal blood pressures (≥90th percentile, or in adolescents aged ≥13 years, systolic blood pressure 120–129 mmHg with diastolic blood pressure <80 mmHg) or hypertension (≥95th percentile or in adolescents ≥13 years systolic blood pressure >130 mmHg with diastolic blood pressure ≥80 mmHg) should have blood pressure confirmed on three separate days. Initial treatment includes dietary modification, increased exercise, and weight control. If high normal blood pressure persists for 3–6 months or in cases of hypertension, pharmacological treatment with angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers should be considered if ACE inhibitor is not tolerated. The goal of treatment is to maintain blood pressures consistently at <90th percentile or <120/80 mmHg in children ≥13 years of age [2, 33].

Dyslipidemia

The atherosclerotic process begins in childhood, and youths with type 1 diabetes may have subclinical cardiovascular disease abnormalities within the first decade of diagnosis. Screening for dyslipidemia should be performed soon after diagnosis and when initial glycemic control has been achieved in all children with type 1 diabetes from age 11 years. If normal results are obtained, this should be repeated every 5 years. If there is a family history of hypercholesterolemia or early cardiovascular disease, or if the family history is unknown, screening should commence as early as the age of 2 years. If LDL cholesterol is <100 mg/dL, a lipid profile testing is suggested every 3 years [2, 91].

The first step of therapy is optimizing glucose control and medical nutrition therapy. For patients aged >10 years, the addition of statin is suggested if despite medical nutrition therapy and lifestyle changes, the patient continues to have LDL cholesterol levels >160 mg/dL or LDL cholesterol levels >130 mg/dL and one or more cardiovascular disease risk factors. (The American Heart Association categorizes children with type 1 diabetes in the highest tier for cardiovascular risk.) The goal of therapy is to achieve a LDL cholesterol value of <100 mg/dL [2].

Nephropathy

Diabetic nephropathy (e.g., albuminuria) most commonly occurs after the onset of puberty and after 5–10 years of diabetes duration. Good glycemic and blood pressure control, mainly as the diabetes duration increases, is important to reduce the risk of nephropathy. Routine screening is important to ensure timely detection and treatment. Annual screening for albuminuria with a random (morning sample to avoid the effects of exercise) spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at >10 years, once the child has had diabetes for 5 years [2]. Estimation of the glomerular filtration rate using equations for serum creatinine level, height, age, and sex at baseline is also recommended and should be repeated on the basis of clinical status. Treatment with an ACE inhibitor or an angiotensin receptor blocker titrated to normalization of albumin excretion should be considered when an elevated urinary albumin-to-creatinine ratio (>30 mg/g) is documented with at least two of three urine samples over a 6-month interval after efforts to improve glycemic control and normalize blood pressure [2].

Retinopathy

Diabetic retinopathy most commonly occurs after the onset of puberty and after 5–10 years of diabetes duration; however, it has been reported in pre-pubertal children and after a diabetes duration of only 1–2 years [2]. Early subclinical retinopathy may exist and can be detected through corneal confocal microscopy by the identification of corneal cellular pathology (lower epithelial and endothelial densities and higher keratocyte density) and small nerve fiber pathology in young patients with type 1 diabetes [92].

An initial dilated and comprehensive eye examination must be performed once youths with type 1 diabetes are aged ≥11 years or after puberty has started, whichever is earlier, in patients with a diabetes duration of 3–5 years. After the initial examination, patients must undergo repeat dilated and comprehensive eye examinations every 2 years or less frequently (every 4 years) on the advice of an eye care professional based on risk factor assessment, including a history of glycemic control with HbA1c levels <8%. Eye examinations could be more frequent if high-risk factors of vision loss are present [2, 33, 91].

Neuropathy

Diabetic neuropathy rarely occurs in pre-pubertal children or after 1–2 years of diabetes. Screening for peripheral neuropathy should start from the age of 11 years with 2–5 years of diabetes duration and annually thereafter [91]. A foot inspection at each medical visit is important to educate youths regarding the importance of foot care [33] (Codner limited care). A comprehensive foot examination should include an assessment of symptoms of neuropathic pain, inspection, palpation of pulses, assessment of reflexes, and determination of proprioception, vibration, and monofilament sensation [2].

Smoking

Smoking is a well-recognized cardiovascular disease risk. In youths with diabetes, additional cardiovascular disease risk factors must be avoided. Smoking increases microvascular and macrovascular complications. For these reasons, smoking avoidance (including cigarettes, other tobacco products, e-cigarettes, and secondhand smoke) is important to prevent microvascular and macrovascular complications and should be part of routine diabetes care [2, 34].

Quality of Life

Although the health-related quality of life of children/adolescents with type 1 diabetes may not be adversely affected compared with that of siblings without diabetes [93], burdens are imposed on children and their parents by a diagnosis of type 1 diabetes mellitus, which affects their health-related quality of life [94]. In general, type 1 diabetes is associated with lower health-related quality of life, higher unemployment rates, and additional sick leaves in adults [95]. Health-related quality of life is a critical diabetes outcome, but discrepancies exist between youth and parent-proxy reports in the Pediatric Quality of Life Inventory. Parents often underestimate their child's health-related quality of life, except in the youngest

children. Although examining both reports is optimal, the youth report should be prioritized, particularly for young children and adolescents [96]. Although no correlation may exist between metabolic control and health-related quality of life in children, lower numbers of hypoglycemic and hyperglycemic episodes were associated with an increase in psychosocial and physical health scores [94].

Type 2 Diabetes

Over the last three decades, the incidence and prevalence of T2D have markedly increased in the pediatric population. Before the 1990s, T2D was rare in children and adolescents in the United States. However, by 1994, T2D had represented up to 16% of new cases of diabetes in children in urban areas; after 1999, the range of new cases of T2D was 8–45%, mainly among minority populations [97]. In the United States, the estimated T2D prevalence per 1000 youths aged 10–19 years increased significantly from 0.34 in 2001 to 0.46 in 2009 to 0.67 in 2017, an absolute increase of 0.32 per 1000 youths and a 95.3% relative increase over 16 years. The greatest absolute increases were observed among non-Hispanic Black and Hispanic youths. The projections of the Centers for Disease Control and Prevention assume a 2.3% annual increase in the prevalence of T2D in people aged <20 years, which will quadruple in 40 years [4].

The diagnosis of childhood T2D is based on the presence of diabetes mellitus in a child who typically shows the following characteristics:

- Overweight or obese (body mass index ≥85th to 94th percentile and >95th percentile for age and sex, respectively)
- A strong family history of T2D
- Residual insulin secretory capacity at diagnosis (reflected by normal or elevated insulin and C-peptide concentrations)
- Insidious onset of disease
- Demonstrated insulin resistance, including polycystic ovarian syndrome or acanthosis nigricans
- Lacking evidence of diabetic autoimmunity
- Higher likelihood of having hypertension and dyslipidemia

Although diabetic ketoacidosis is more frequent in type 1 diabetes, patients with T2D may occasionally have this presentation [31].

Testing to detect prediabetes or T2D should be considered in the following cases [2, 4]:

- Children and adolescents aged 10 years or at onset of puberty (if it occurs at a younger age)
- Children and adolescents who are overweight or obese (body mass index ≥85th percentile for age and sex, weight for height >85th percentile, or weight >120% of the ideal for height)
- Children and adolescents with one or more of the following additional risk factors for diabetes:
  - Family history of T2D in first- or second-degree relatives
  - Native American, African–American, Latino, Asian American, or Pacific Islander
  - Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight)
  - Maternal history of diabetes or gestational diabetes mellitus during gestation

If the test results are normal, repeat testing at a minimum of 3-year intervals or more frequently if BMI is increasing. Fasting plasma glucose level, 2-h plasma glucose level during oral glucose tolerance test, and HbA1c level can be used to test for prediabetes or diabetes in children and adolescents. Pediatric patients with overweight or obesity in whom T2D is considered should have a panel of pancreatic autoantibodies to exclude the possibility of type 1 diabetes [2, 98].

Pathophysiology of T2D Mellitus

Insulin resistance in muscle, fat, and liver, with progressive beta cell failure, and ongoing loss of insulin secretion in response to glucose characterize T2D mellitus. The following risk factors associated with this disorder can affect individuals beginning in childhood:

- **Obesity and insulin resistance**. Insulin resistance produces hyperinsulinism, and unsuccessful compensation from increased insulin secretion results in glucose intolerance and T2DM [99].
- **Intrauterine environment.** Poor intrauterine growth is associated with the subsequent development of metabolic syndrome and T2D. The effects of poor nutrition in early life produce changes in glucose-insulin metabolism, such as reduced capacity for insulin secretion and insulin resistance [100].
- **Exposition to gestational diabetes.** Maternal gestational diabetes is independently associated with a subsequent risk of T2D in offspring in the first 30 years of life; the risk is approximately threefold higher than among offspring of mothers without diabetes [101].
- **Ethnicity.** Ethnic differences in diabetes prevalence persist, even after adjustment for lifestyle and other risk fac-

tors. Diabetes mellitus is more likely (relative to Caucasians) among Asians, Native Americans, and Hispanics [102].

- **Sex and puberty.** Puberty represents a state of insulin resistance. This developmental stage is accompanied by a 30% decrease in insulin sensitivity and a compensatory increase in insulin secretion. The mean age at diagnosis of T2D in children is between 12 and 16 years, corresponding to the peak of adolescent growth. Girls are 1.5- to 3-fold more likely than boys to develop T2D as children or adolescents [103].
- **Family history.** Between 74 and 100% of children with T2D have a first- or second-degree relative with T2D. The lifetime risk is 40% if one parent is affected and 70% if both parents are affected [104].
- **Genetics.** The identification of the genetic factors involved in pediatric T2D has been a great challenge. In adults, several association studies have been conducted in which numerous SNPs have been shown to contribute to the risk of the disease; however, these SNPs currently account for only approximately 20% of heritability. By contrast, only few studies have involved pediatric patients, in whom the early onset of the disease may be due in part to greater genetic susceptibility, which makes them less tolerant of environmental aggressors. In this sense, a strong familial history of the disease suggests the involvement of genetic factors. We reported that the heritability of pediatric-onset T2D in Mexican youths was as high as 0.50 [105]. Likewise, the most important diabetes susceptibility variants reported to date are SNPs in the *TCF7L2* gene, which have strong associations with T2D in multiple ethnic populations [106]. Dabalea et al. identified *TCF7L2* variants associated with an increased risk of T2D among African–American youths [107]. In addition, we recently reported an association between SNPs in *SLC16A11* (rs13342232) and pediatric-onset T2D in the Mexican population. Our research group reported that SNPs previously associated with obesity, such as *ADORA/rs903361*, *CADM2/rs13078807*, *GNPDA2/rs10938397*, *VEGFA/rs6905288*, and *FTO/rs9939609*, were associated with an increased risk of pediatric-onset T2D in the Mexican population [108].

- The combination of multiple SNPs improves the prediction of the risk of T2D in youths with a modest significance. On the contrary, clinical factors such as body mass index and family history of T2D continue to have the highest predictive value in some populations [109].

Treatment

The treatment goals for T2D are the same as those for type 1 diabetes. In addition to blood glucose control, treatment must include attention to metabolic disorders such as obesity, hypertension, and dyslipidemia [2]. Lifestyle changes should be initiated at the time of diagnosis of T2D [110]. Education should focus on behavioral changes (diet and activity) and education on the administration of oral hypoglycemic agents and insulin as needed. The education and treatment team for a patient with T2D should ideally include a nutritionist, psychologist and/or social worker, and an exercise physiologist [3, 110].

The entire family will need education to understand the principles of the treatment of T2D and the critical importance of lifestyle changes for the entire family to successfully manage a youth with T2D [110].

Nutritional and Exercise Management

The aims of nutritional management must be focused on a multidisciplinary, family-centered, culturally appropriate approach that promotes the achievement of normal glycemia and HbA1c levels, preventing further weight gain in patients with a body mass index in the 85th–95th percentile or achieving weight loss for those with a body mass index >95th percentile while maintaining a normal linear growth. Physicians and dietitians should focus on nutritional counseling for children with T2D at the time of diagnosis and as a part of ongoing management [49, 51].

The entire family should be included in the education because caregivers influence the child's food intake and physical activity. The dietary recommendations should target dietary modifications and should be culturally appropriate, sensitive to family resources, and provided to all caregivers [49, 51, 110].

Healthy eating patterns should be encouraged, with an emphasis on consuming nutrient-dense, high-quality foods and reducing calorie-dense, nutrient-poor foods [111]. The dietary modifications should include the following:

- Eliminating sugar-containing soft drinks and juices and substitution of water, diet soft drinks, and other calorie-free beverages, which can result in substantial weight loss [110, 112]. FDA-approved non-nutritive sweeteners can be used, as they may help consumers limit their carbohydrate and energy intake as a tactic to manage blood glucose and/or weight [113].
- Increasing fruit and vegetable intake, which is known to confer several health benefits [110, 114].
- Reducing the use of processed, prepackaged, and convenience foods and the intake of foods made from refined, simple sugars, such as processed candy and high-fructose corn syrup [110].
- Control portions. Food and snacks should be served in a plate or bowl and not eaten directly from a box or can [110].

- Reducing the number of meals eaten away from home [110].
- Changing staple foods from enriched white rice and white flour to brown rice and whole-grain items with lower glycemic index values to promote gradual and sustainable energy elevations with meals [110].
- Changing family diet behaviors: limiting the availability of high-fat, high-caloric-density foods and drinks in the home; teaching families to interpret nutrition fact labels; emphasizing healthy parenting practices related to diet and activity; encouraging positive reinforcement of all goals achieved and avoiding blame for failure; and promoting that meals should be eaten on schedule, in one place, preferably as a family unit, and with no other activities (e.g., television, computer, or studying) [110].

In addition to following the above-mentioned recommendations, an individualized meal plan incorporating low-fat energy choices and carbohydrate management and the substitution of high- for low-glycemic-index foods may help control appetite, weight loss, blood glucose targets, and lipid levels [51].

Increasing daily physical activity to 60 min of moderate-to-vigorous exercise is an important component of treatment and a key strategy to increase energy expenditure; exercise can be completed in multiple shorter sessions. Promoting physical activity as a family event, including daily efforts to be more physically active, such as using stairs instead of elevators, walking or bicycling to school and shopping, and doing house and yard work, can help promote adherence to the plan. Limiting sedentary behaviors such as television viewing and computer use to <1 h a day has been shown to be an effective way of increasing daily physical activity and help maintain or achieve a healthy weight in children [51, 110].

Youth with overweight/obesity and T2D and their families should be provided with developmentally and culturally appropriate comprehensive lifestyle programs that are integrated with diabetes management to achieve a 7–10% decrease in excess weight [98].

Smoking and Tobacco Use

Cigarette smoking is damaging to all youths, but patients with diabetes are especially vulnerable to the negative health costs of smoking as a result of their compromised health status and disease and treatment-related complications [110, 114].

Additional research is needed to develop and study the efficacy of interventions specifically targeting smoking among youths with T2D within health-care settings. Patients should be asked at each visit if they smoke and counseled against beginning smoking. Youths who do smoke should be counseled on the importance of smoking cessation and provided resources for support [110].

Glycemic Monitoring

Limited evidence shows that self-monitored blood glucose has an impact on glycemic control in individuals with T2D. Blood glucose self-monitoring should be performed regularly, and the frequency should be individualized and include a combination of fasting and postprandial glucose measurements with a regularity based on the degree of glycemic control and available resources. Once glycemic goals have been achieved, limited at-home testing is needed; at most, several fasting and postprandial values per week are satisfactory. If values consistently exceed the target range, more frequent testing should be recommended because a change in therapy might be needed. During acute illness or when symptoms of hyperglycemia or hypoglycemia occur, patients should undergo more frequent testing and be in contact with their diabetes care team for advice [110].

Glycemic Targets

Glycemic status should be assessed every 3 months. A reasonable HbA1c target for most children and adolescents with T2D is <7% (53 mmol/mL). More stringent targets (e.g., <6.5% [48 mmol/mol]) may be appropriate for selected individual patients if they can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with a short diabetes duration and less severe β-cell dysfunction and those treated with lifestyle or metformin alone and achieve significant weight improvement [2]. Self-monitoring of blood glucose needs to be individualized depending on the intervention for T2D [98, 115].

Pharmacological Treatment

The treatment of diabetes in children and adolescents cannot simply be derived from the pharmacological management that is routinely provided to adults with diabetes. The epidemiology, pathophysiology, developmental considerations, and response to therapy in pediatric-onset diabetes are different from those of adult diabetes [2]. A more aggressive phenotype of T2D exists in the pediatric population, which predisposes patients to an earlier dependence on insulin treatment and a presentation of chronic complications in an earlier term [98].

The aims of therapy for pediatric-onset T2D are to improve glycemia, prevent acute and chronic complications, prevent metabolic decompensation, improve insulin sensitivity and endogenous insulin secretion, and if possible, restore glucagon and incretin physiology [98].

Great uncertainty remains about the use of many novel drug treatments in the pediatric population, in whom the absence of information about safety limits their use [116]. The glycemic goals can usually be accomplished with metformin and basal insulin, alone, or in combination. The initial treatment is determined by symptoms, severity of hyperglycemia, and presence or absence of ketosis/ketoacidosis [76, 110].

Metformin

Metformin is a biguanide that increases insulin-mediated glucose uptake in the peripheral tissues and decreases hepatic glucose production, thereby promoting a decrease in plasma glucose levels [117, 118]. Currently, metformin is the only oral hypoglycemic agent approved for use in children with T2D [119].

Metformin monotherapy treatment should begin at 500 mg daily. The dose should be titrated by 500 mg once per week over 3–4 weeks to the maximal dose of 1000 mg twice daily. Blood glucose self-monitoring should be performed regularly and should be individualized on the basis of the degree of glycemic control and available resources [98, 110].

Metformin is associated with several gastrointestinal side effects, mainly nausea, abdominal pain, and headache; therefore, some patients may require slower dose escalation or may not be able to tolerate the maximum dose. Extended-release metformin preparations may have less frequent gastrointestinal side effects and are now currently available in tablet and suspension forms. Contraindications for metformin include renal and hepatic insufficiency, cirrhosis, hepatitis, and cardiopulmonary insufficiency, as metformin can lead to lactic acidosis in this setting. In addition, the absorption of vitamin B12 and folic acid can be impaired in patients taking metformin, and vitamin B12 deficiency may frequently occur in patients with anemia and peripheral neuropathy. Therefore, children and adolescents taking metformin should be advised to take multivitamins daily [115, 120].

For children on oral treatment, discontinuation of metformin 24 h before a major surgery (lasting at least 2 h) and on the day of surgery for a minor surgery is recommended. Hourly blood glucose monitoring is also recommended. If the blood glucose level is >180 mg/dL, IV insulin should be administered (as for elective surgery) to normalize levels; or subcutaneous insulin, if the patient is to undergo a minor procedure [76, 80].

In patients with ketosis, ketonuria, or ketoacidosis, treatment with subcutaneous or intravenous insulin should be initiated to rapidly correct the metabolic abnormality. Once a day of intermediate-acting or basal insulin (0.25–0.5 units/kg starting dose) is generally effective in attaining metabolic control. Metformin can be started along with insulin; once acidosis is resolved, the transition to metformin monotherapy can usually be achieved safely over 2–6 weeks [98].

If the patient fails to achieve a target HbA1c of <6.5% within 3–4 months on metformin monotherapy, the addition of basal insulin should be considered. If the target is not achieved on a combination of metformin and basal insulin (up to 1.2 units/kg), prandial insulin should be initiated and titrated to reach a target HbA1c level of <6.5% [110].

Glucagon-like peptide-1 analogs

Glucagon-like peptide-1 (GLP-1) is a hormone produced by the gut enteroendocrine cells, specifically the L cells of the small intestine, and is secreted after the ingestion of nutrients. Therefore, it controls meal-related glycemic excursions through augmentation of insulin levels and inhibition of glucagon secretion. GLP-1 also improves insulin biosynthesis and secretion and decreases β-cell apoptosis. In addition, it inhibits gastric emptying and food intake, actions maximizing nutrient absorption while limiting weight gain [120].

Liraglutide, a GLP-1 analog, has been recently approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for children and adolescents aged ≥10 years who have T2D according to the ELLIPSE Study data [121]. Liraglutide is efficacious for improving glycemic control and is started at a dose of 0.6 mg subcutaneously once daily, with incremental doses every 1–2 weeks or longer until fasting glucose targets are achieved to a maximum of 1.8 mg daily [115, 121]. Adverse effects with the use of liraglutide include nausea, vomiting, diarrhea, addominal pain and headache. In addition, a higher frequency of mild hypoglycemic episodes was also found [121].

If glycemic targets are no longer met with metformin (with or without basal insulin), liraglutide therapy should be considered in children 10 years of age or older if they have no past medical history or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 [39].

Insulin

When the individualized glycemic target can no longer be met with metformin alone or if metformin intolerance or renal or hepatic insufficiency develops, insulin therapy should be initiated alone or in combination with metformin unless metformin is contraindicated. The long-acting insulin analogs (glargine, detemir, or degludec) may be preferred [122].

Patients with ketosis, ketoacidosis, or a glucose concentration ≥200 mg/dL or HbA1c level ≥8.5% require a period of insulin therapy until glycemia has been restored to near-normal [2]. These patients require basal insulin (0.25–0.5 units/kg/day), and the dose can be adjusted according to the blood glucose values. Long-acting once daily insulin preparations could be administrated at bedtime [110]. Multiple daily injections with prandial short-acting insulin should be recommended in youths receiving high doses of basal insulin (up to 1.5 units/kg/day) [115, 122, 123].

Ongoing trials are evaluating the effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sulfonylureas in children and adolescents with T2D. The results from these trials would soon expand the availability of pharmacological options to youths with T2DM [115, 122, 124].

Bariatric Surgery

Bariatric surgery, also called metabolic surgery, including Roux-in Y gastric bypass, vertical sleeve gastrectomy, laparoscopic adjustable gastric banding, laparoscopic gastric plication, and biliopancreatic, has been shown to significantly reduce weight, BMI, and cardiovascular comorbidities [2]. In addition, bariatric surgery has been shown to improve glucose metabolism in adolescents and adults with morbid obesity, which seems to be independent of weight loss, suggesting a direct hormonal effect [125].

The selection criteria for adolescent bariatric surgery include BMI ≥35 kg/m^2 and severe comorbidities such as T2D mellitus [98, 125, 126]. Recent results have demonstrated the remission of T2D and other comorbidities in nearly all youths after undergoing bariatric surgery [126–128], with attainment of HbA1c targets exceeding that observed with medical therapy [129]. A study conducted in México in adolescents with morbid obesity and T2D with gastric sleeve presented complete remission [130].

All bariatric procedures have an effect on glucose metabolism. The mechanisms responsible for improved glycemic control after bariatric surgery are thought to be associated with decreased nutritional intake, weight loss, and/or hormonal changes. The metabolic abnormalities associated with T2D mellitus can be reversed by bariatric surgery in most patients [125]. Roux-in-Y gastric bypass, the traditional surgical procedure for weight loss, can cause significant morbidity and mortality; however, newer techniques, which appear to be safer, include gastric banding and sleeve gastrectomy [110, 128].

Comorbidities

In children and adolescents with T2D and insulin resistance, the presence of multiple cardiovascular risk factors is likely to be associated with earlier severe complications [51]; thus, regular follow-up is essential to monitor weight and glycemic control and to prevent and address the development of diabetes-related complications such as hypertension and dyslipidemia [49, 51]. Hyperglycemia, dyslipidemia, and hypertension are contributors to the acceleration of atherosclerosis in T2D, along with oxidative stress, glycation of vascular proteins, and abnormalities in platelet function and coagulation. Endothelial dysfunction is an early sign of increased risk of cardiovascular disease, is predictive of cardiovascular events, and occurs in obese children relative to their level of obesity and degree of insulin resistance [110].

Blood pressure measurements, lipid panel, liver enzymes, albumin excretion, and dilated eye examinations should be performed at diagnosis because comorbidities may already be present at the time of diagnosis in youths with T2D. Then, the screening guidelines and treatment recommendations are similar to those for patients with type 1 diabetes. In addition, patients with T2D may need attention to other disorders, including polycystic ovary disease, obesity, sleep apnea, hepatitis steatosis, orthopedic disorders, and psychosocial concerns [2, 98].

Obesity

Weight loss and exercise both improve insulin resistance and glycemia, so the assessment of body mass index and pattern of weight gain should be considered a routine part of monitoring in youths with T2D, as obesity has deleterious associations with morbidity independent of insulin resistance and diabetes [110].

Hypertension

Hypertension is associated with endothelial dysfunction, arterial stiffness, and increased risk of both cardiovascular and kidney disease [131]. According to the TODAY study [132], hypertension was present in 13.6% of 699 US youths at a median diabetes duration of 7 months. Higher rates have been reported in Australia, with 36% of youths with T2D having hypertension within 1.3 years of diagnosis [133].

Several recommendations should be followed, such as measuring blood pressure with an appropriate-sized cuff at every clinic visit and normalizing the results for sex, height, and age. The initial treatment for blood pressure that is consistently ≥95th percentile at three visits should consist of efforts at weight loss, dietary salt restriction, and increased physical activity [110]. If blood pressure is still ≥95th percentile after 6 months, initiation of angiotensin-converting enzyme inhibitor therapy should be considered to achieve blood pressure values <90th percentile [134]. If the angiotensin-converting enzyme inhibitor is not tolerated due to adverse effects, an angiotensin receptor blocker is often used as a second-line therapy [98, 110].

Nephropathy

Early diabetic kidney disease (microalbuminuria and renal hyperfiltration) is common in adolescents with T2D and carries a higher risk of progression than the adult-onset type. Diabetic kidney disease is characterized by a long period with no signs of disease. One challenge in preventing the disease is the difficulty of identifying it at an early stage [135].

Albuminuria should be evaluated at diagnosis and annually thereafter. The definition of microalbuminuria used by the American Diabetes Association is either an albumin-to-creatinine ratio (ACR) of 30–299 mg/g in a spot urine or timed overnight sample or 24-h sample collections, with an albumin excretion rate of 20–199 μg/min. An elevated value may be secondary to exercise, smoking, menstruation, or

orthostasis [110]. Abnormal screening tests should be repeated, as albuminuria may be transient. Therefore, the diagnosis of persistent abnormal microalbumin excretion requires the documentation of two of three consecutive abnormal values obtained on different days [91, 98, 110].

Non-diabetes-related causes of renal disease should be excluded, and consultation must be sought, especially if macroalbuminuria (ACR > 300 mg/g) is present [110]. Angiotensin-converting enzyme inhibitors are the agents of choice because of their beneficial effects for preventing diabetic nephropathy, even with normal blood pressures [103]. Albumin excretion should be monitored at 3- to 6-month intervals, and therapy doses should be titrated to achieve normal albumin-to-creatinine ratios as much as possible [110]. Non-diabetes-related causes of renal disease especially in the presence of ACR >300 mg/g can be referred to nephrologists [98].

Dyslipidemia

Hypertriglyceridemia and decreased HDL cholesterol levels are hallmarks of dyslipidemia, which is characteristic of insulin resistance and T2D in children and adolescents. Testing for dyslipidemia should be performed soon after diagnosis when blood glucose control has been achieved and annually thereafter. The target levels are as follows [110]:

- LDL cholesterol <100 mg/dL (2.6 mmol/L)
- HDL cholesterol >35 mg/dL (0.91 mmol/L)
- Triglycerides <150 mg/dL (1.7 mmol/L)

In the case of persistent dyslipidemia despite dietary and exercise counseling, pharmacotherapy may be initiated. Statin therapy has been shown to be as safe and effective in children as in adults and should be the first pharmacological intervention, beginning with the lowest available dose. Treatment with a fibric acid medication should also be considered when fasting triglycerides are >400–600 mg/dL [98, 110].

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS) is increasingly recognized in adolescents as part of insulin resistance syndrome. Adolescents with PCOS had an approximately 40% reduction in insulin-stimulated glucose disposal compared with body composition-matched non-hyperandrogenic control subjects [98, 136].

Reducing insulin resistance with weight loss, exercise, and metformin therapy improves ovarian function and increases fertility. Menstrual history taking should be performed for all girls with T2D at diagnosis and at each visit. An evaluation for PCOS should be considered if primary or secondary amenorrhea, hirsutism, and/or significant acne are found. PCOS is diagnosed on the basis of the presence of oligomenorrhea or amenorrhea with biochemical or clinical evidence of hyperandrogenism, with or without evidence of polycystic ovaries. Girls receiving diabetes treatment should also be counseled that fertility may improve as a result and that proper birth control should be used to prevent any unwanted pregnancy [98, 110].

Non-alcoholic Fatty Liver Disease

Hepatic steatosis is present in 25–50% of adolescents with T2D, and more advanced forms of non-alcoholic fatty liver disease (NAFLD), such as non-alcoholic steatohepatitis (NASH), have become increasingly common and are associated with progression to cirrhosis, portal hypertension, and liver failure. NAFLD is now the most frequent cause of chronic liver disorders among obese youths [110].

Interpretation of ALT levels should be based upon the sex-specific upper limits of normal in children (22 U/L for girls and 26 U/L for boys) and not on individual laboratory upper limits of normal. NAFLD/NASH or other causes of chronic hepatitis should be considered for persistently (>3 months) elevated ALT levels >3 times the upper limit of normal. The patients should be referred to the gastroenterology department if liver enzymes remain elevated >3 times [98].

Weight loss improves NAFLD, and metformin has been shown to improve liver enzymes and liver steatosis in insulin-resistant adolescents [137]. T2D therapies that improve insulin resistance appear to improve NAFLD and are therefore the standard approach to youths with both NAFLD and T2D. However, owing to the potential for progression to NASH, fibrosis, and cirrhosis, ongoing monitoring of liver enzymes is recommended in youths with T2D. Referral for biopsy is recommended if enzymes remain markedly elevated despite weight loss and/or diabetes therapies [110].

Obstructive Sleep Apnea

Obstructive sleep apnea is common in obese youths, but its prevalence in pediatric T2D has not yet been well documented. However, the prevalence is likely high, as the prevalence in adults is between 70 and 90% [138, 139]. Obstructive sleep apnea not only causes poor sleep quality and daytime sleepiness but also has clinical consequences, including hypertension, left ventricular hypertrophy, and increased risk of renal and cardiovascular disease [98, 110].

Youths with T2D can be screened for obstructive sleep apnea by questioning them about snoring, sleep quality, apnea, morning headaches, daytime sleepiness, and enuresis. If symptoms are suggestive, a diagnosis is made through a formal sleep study and referral to a sleep specialist [110].

Depression

Youths with T2D are at increased risk of major clinical depression, which is associated with poor adherence to diabetic treatment recommendations. Signs include depressed mood, markedly diminished interest or pleasure, increased or decreased appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, and recurrent thoughts of death [98, 110].

Youths with T2D, particularly those with frequent emergency department visits or poor glycemic control, should be assessed for depression at diagnosis and periodically thereafter [110]. Patients identified as depressed should be referred to appropriate mental health-care providers experienced in addressing depression in youths [140].

Additional Health Problems Related to Obesity and T2D

All patients with T2D may have additional health problems related to the disease, such as orthopedic problems resulting in diminishing physical activity, pancreatitis, cholecystitis, pseudotumor cerebri, and deep tissue ulcers. These additional health problems should be screened at diagnosis and rescreened periodically [110].

Transition from Pediatric to Adult Care

The care and close supervision of diabetes management are increasingly shifted from parents and other adults to the youth with type 1 or 2 diabetes over the course of childhood and adolescence [141]. The shift from pediatric to adult health care is inevitable, and the transition is always difficult regardless of age. However, in some places, more than half of patients continued to receive pediatric care even after the age of 30 years [142].

The transition often occurs abruptly as older teens enter the next developmental stage, referred to as emerging adulthood, and a lack of consistent care may follow the transition in 30–40% of patients [76, 141]. The transition is a period associated with deterioration in glycemic control; increased occurrence of acute complications, psychosocial, emotional, and behavioral challenges; and the emergence of chronic complications [76, 141].

During this period, youths with T2D often struggle with becoming fully responsible for their diabetes care; therefore, discussion about the transition during the several visits before it occurs may help prepare the patient [76, 141]. Health-care providers and families should begin to prepare youths with diabetes in early- to mid-adolescence and at least 1 year before the transition to adult health care, and both pediatricians and adult health-care providers should assist in providing support for the teen and emerging adult [141].

Concluding Remarks

- The pathophysiology and diagnostic criteria for diabetes mellitus are the same in children and adults.
- However, issues specific to early childhood diabetes include changes in insulin sensitivity due to growth and development, dependence on care, and neurological susceptibility to changes in glucose.
- The younger age of presentation of diabetes in pediatric patients causes a longer disease exposure, with the development of chronic complications at an early age; therefore, close surveillance is required.
- Children are not small adults; thus, treatment should be adapted to age-related physiological changes.
- The only pharmacological treatments approved for children and adolescents are insulin for type 1 diabetes mellitus, metformin, liraglutide, and insulin for T2D mellitus and sulfonylureas for some types of neonatal diabetes. Pediatric patients with T2D could also be candidates for bariatric surgery.

Multiple-Choice Questions

1. What is the most common type of diabetes mellitus in children and adolescents?
   (a) **Type 1 diabetes mellitus**
   (b) Type 2 diabetes mellitus
   (c) Monogenic diabetes
   (d) MODY
   (e) Neonatal diabetes

   Although type 2 diabetes is occurring more frequently in pediatric patients and other forms such as neonatal diabetes are unique to this age range, type 1 diabetes is the predominant form in this age group.
2. Which of the following clinical features raises the suspicion of monogenic diabetes?
   (a) Diabetic ketoacidosis in a school-age child
   (b) A random plasma glucose level ≥200 mg/dL in a child with obesity, acanthosis nigricans, and a family history of type 2 diabetes
   (c) **Diabetes in the first 6 months of life, a strong family history of type 2 diabetes in a nonobese patient or low-risk ethnic group, and fasting glycemia of 100–150 mg/dL**
   (d) Neonatal hyperglycemia in infants with elfin facies, low birth weight, and skin abnormalities
   (e) Diabetes mellitus associated with autoantibodies

   Monogenic diabetes is characterized by impaired insulin secretion by pancreatic beta cells caused by a single gene mutation. These forms of diabetes represent less than 5% of patients with diabetes and are charac-

terized by onset generally before age 25 years, without clinical features of insulin resistance in type 2 diabetes and with negative associated autoantibodies.

3. What are the blood glucose and HbA1c goals for type 1 diabetes mellitus across all pediatric age groups?
   (a) Blood glucose level of 100–150 mg/dL before a meal and 100–125 mg/dL at bedtime/overnight, and HbA1c level of <8.5% in infants, <8.0% in school-children, and <7.5% in adolescents
   (b) **Blood glucose of 90–130 mg/dL before a meal and 90–150 mg/dL at bedtime/overnight, and HbA1c level of <7.5% across all pediatric age groups**
   (c) Blood glucose level of <100 mg/dL before a meal, <140 mg/dL after a meal, and 100–125 mg/dL at bedtime/overnight, and HbA1c level of <6.5% across all pediatric age groups
   (d) The lowest HbA1c level is possible regardless of the degree of hypoglycemia
   (e) Blood glucose level of <200 mg/dL after a meal and HbA1c level of <8.5% across all pediatric age groups

   Glycemic control needs to be of a sufficient degree to prevent diabetes-related complications; however, strict glucose levels carry the risk of hypoglycemia. Although young children were previously thought to be at risk of cognitive impairment after episodes of hypoglycemia, current data have not confirmed this notion. Hence, current standards recommend lowering glucose to the safest possible level to prevent chronic complications.
4. In an oral glucose tolerance test, what is the glucose load used to diagnose diabetes mellitus in children and adolescents?
   (a) 1.75 g of anhydrous glucose per kg body weight, with a maximum of 50 g
   (b) 1.50 g of anhydrous glucose per kg body weight, with a maximum of 75 g
   (c) 1.50 g of anhydrous glucose per kg body weight, with a maximum of 50 g
   (d) 1.75 g of anhydrous glucose per kg body weight, with a maximum of 65 g
   (e) **1.75 g of anhydrous glucose per kg body weight, with a maximum of 75 g**

   The loading of anhydrous glucose in the oral glucose tolerance test must be calculated per body weight, with a maximum adult load of 75 g. In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.
5. Which of the following is the best treatment option for mild hypoglycemia in pediatric patients with type 1 diabetes?
   (a) Intravenous 10% glucose, 2–3 mL/kg
   (b) 10–15 g of oral glucose using complex carbohydrates
   (c) **10–15 g of oral glucose using simple carbohydrates**
   (d) Glucagon 10–30 μg/kg of body weight
   (e) Switching off the insulin pump

   Milder hypoglycemia should be treated with 10–15 g of oral glucose in the form of simple carbohydrates such as glucose tablets or sweetened fluids such as juice. Subsequently, blood glucose levels should be retested in 10–15 min. In case of an inadequate response, treatment should be repeated and blood glucose levels should be retested in another 10–15 min to confirm that a glucose level of 100 mg/dL has been reached. In some circumstances, this should be followed by administration of additional complex carbohydrates to prevent the recurrence of hypoglycemia. Intravenous glucose and glucagon are used in more severe hypoglycemia.
6. Which treatment has been observed to be effective at preventing beta cell failure in the honeymoon phase?
   (a) **Insulin**
   (b) Glucagon
   (c) Metformin
   (d) Sulfonylureas
   (e) None of the above

   Early small doses of insulin have been observed to be effective at preventing beta cell failure in slowly progressive type 1 diabetes, and they have been recommended for patients with positive antibodies. During the honeymoon phase, the insulin requirement decreases, and basal insulin of 0.2–0.6 units/g/day during this phase may preserve beta cell function.
7. If diabetes occurs at puberty and the patient has obesity, insulin resistance data, and a genetic background for T2DM, what type of diabetes are we required to rule out?
   (a) Neonatal diabetes
   (b) Type 1 diabetes mellitus
   (c) Monogenic diabetes
   (d) MODY
   (e) **Type 2 diabetes mellitus**

   The clinical data that usually support the presence of T2DM are overweight or obesity, first- or second-degree relatives with diabetes, presence of acanthosis nigricans, hypertension, dyslipidemia, non-alcoholic fatty liver, exposure to gestational diabetes, low height or macrosomia at birth, obstructive sleep apnea syndrome, and polycystic ovary syndrome. C-peptide levels ≥0.5 ng/dL may be an indirect marker that endogenous insulin secretion still exists and therefore lead to T2DM. However, this may be decreased at the beginning of diagnosis and late illness.
8. Which of the following is true regarding insulin therapy in patients with type 1 diabetes mellitus?
   (a) The insulin requirements are the same across all age groups (0.5 units/kg/day).

(b) Treatment regimens with two doses of insulin, multiple doses of insulin, or continuous infusion are equally effective.
(c) To avoid hypoglycemia, the short-acting dose of insulin should consider the amount of food to be consumed without taking into account glucose levels.
(d) The insulin pump is indicated only in patients for whom control with multiple injections is not achieved.
(e) **The insulin scheme should mimic natural production, with basal insulin to maintain glucose levels between meals and rapid insulin to cover carbohydrates and normalize glucose.**

Insulin requirements range from 0.25 to 1.5 units/kg/day according to age and pubertal development. Intensive management with the use of multiple-dose insulin and/or continuous subcutaneous insulin infusion in children and adolescents with type 1 diabetes mellitus showed a marked decline in HbA1c level and chronic complications. The primary goal of treatment is to mimic natural insulin secretion, with basal insulin to maintain near-normal blood glucose levels between meals and short-acting insulin to cover the carbohydrates consumed during meals and normalize blood glucose levels. Insulin pumps have become increasingly available to patients with diabetes, and experts highlight their use as the chosen treatment option for many people across all age groups living with type 1 diabetes.

9. How should the total energy intake be distributed in the management of type 1 diabetes mellitus?
(a) Restricted energy intake with carbohydrate 50%, fat 30%, and protein 20%
(b) Normal energy intake with a low-carbohydrate intake of 20% to prevent hyperglycemia
(c) Normal energy intake with low fat to prevent ketosis
(d) **Normal energy intake with carbohydrate 45–65%, fat 30–35%, and protein 15–25%**
(e) Restricted energy intake with carbohydrate 60%, fat 25%, and protein 15%

Energy intake should be sufficient to achieve optimal growth and maintain an ideal body weight. The total daily energy intake should be distributed as follows: carbohydrate 45–65%, fat 30–35%, and protein 15–25%. Carbohydrates should not be restricted, as they are essential for growth.

10. Which pharmacological treatment(s) is/are approved to treat type 2 diabetes in children and adolescents?
(a) **Liraglutide, metformin, and insulin**
(b) Thiazolidinedione and metformin
(c) Same as in adults
(d) Insulin only
(e) SGLT2 inhibitor and metformin

Metformin is the only oral hypoglycemic agent approved for daily use in children with type 2 diabetes. Treatment with metformin monotherapy should begin at 500 mg daily. The dose should be titrated by 500 mg once per week over 3–4 weeks to the maximal dose of 1000 mg twice daily. If the patient fails to achieve a target HbA1c level of <6.5% within 3–4 months on metformin monotherapy, the addition of basal insulin should be considered. Liraglutide is a GLP-1 analog approved by the FDA and EMA in 2019 for children and adolescents aged ≥10 years with T2DM.

11. Which of the following is true about follow-up for pediatric patients with type 2 diabetes?

(a) Nutritional management must be focused on achieving normal glycemia regardless of the body mass index.
(b) Moderate-to-vigorous exercise for 15–30 min twice per week is recommended.
(c) **The examination of comorbidities should be performed at diagnosis.**
(d) Patients with type 2 diabetes do not need to self-monitor their blood glucose levels.
(e) The target levels for dyslipidemia are LDL-C <200 mg/dL, HDL-C >35 mg/dL, and triglycerides <150 mg/dL.

Nutritional management must be focused on achieving normal glycemia and HbA1c levels, preventing further weight gain, or achieving weight loss while maintaining normal linear growth. Patients should increase their daily physical activity to 60 min of moderate-to-vigorous exercise. Blood pressure measurements, lipid panel, albumin excretion, and dilated eye examinations should be performed at diagnosis because comorbidities may already be present at that time. Blood glucose self-monitoring should be performed regularly. The target levels for dyslipidemia are LDL-C <100 mg/dL, HDL-C >35 mg/dL, and triglycerides <150 mg/dL.

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Suggested Reading

ISPAD Clinical Practice Consensus Guidelines 2018. https://www.ispad.org/page/ISPADGuidelines2018. This compendium of consensus guidelines contains updates about significant advances in scientific knowledge and clinical care for pediatric and adolescent patients with diabetes mellitus.

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Pregnancy: Pregestational and Gestational Management

65

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Introduction

Gestational diabetes (GD) is defined as an alteration in carbohydrate metabolism diagnosed for the first time in the second or third trimester of gestation, it being clear that the diagnosis of same during the first trimester indicates preexisting type 1 or 2 diabetes. The growing index of obesity is a global problem, where the main factors that unleash it are bad eating habits and sedentary lifestyle. Obesity in pregnancy is a risk factor for developing diabetes, which goes hand in hand with an increased maternal and fetal risk and hypertensive disorders. Women of a reproductive age are not the exception in regard to obesity; the U.S. National Health and Nutrition Survey (1999–2008) reveals that more than one third of the women of reproductive age are obese, and 7.6% of these women are extremely obese, with body mass indices (BMIs) equal or greater than 40; the percentage of pregnant women with obesity is estimated between 18 and 38% [1, 2]. In regard to Mexico, we have one of the highest prevalence of overweight, obesity, and diabetes in the world. Studies based on the Encuesta Nacional de Salud y Nutrición (ENSANUT, National Health and Nutrition Survey, in English) 2012 show that in the last decades, an increase has been observed in body mass and waist perimeter in the population, with a higher prevalence among young Mexican women of reproductive age, compared with other populations [3], and these changes evidently have attention-getting metabolic repercussions, above all because the female reproductive population is implicated. In consequence, pregnancy-associated diabetes is more and more frequent, and it is estimated that it significantly complicates around 1–16% of all births worldwide, depending on the population studied. The prevalence of GD has a variation directly proportional to the prevalence of type 1 diabetes (T1D) and type 2 diabetes (T2D), depending on the population under study. Other estimates indicate that 6–7% of pregnancies are complicated by this disease and that approximately 90% of the cases are represented by women with T1D and T2D. It has also been established that the highest prevalence is found among Hispanics, Afro-Americans and natives of America, Asia, and the Pacific islands [4]. Suffering GD significantly increases the risk of adverse results of the pregnancy compared with normal pregnancy: congenital malformations in 5% against 2% in the general population, perinatal mortality in 2.7% against 0.72%, premature birth in 25% against 6%, and fetal macrosomia in 54% against 10% [5]. This pregnancy complication is a growing problem for public health, with genetic, environmental, and social determinants; but obesity has a major importance as a risk factor. There exists the hypothesis that fetal overnutrition during maternal exposure GD is associated with increased overall abdominal adiposity, and a more central fat distribution pattern in 6- to 13-year-old children from a multi-ethnic population [6]. Therefore, the combination of diabetes and pregnancy is not a desirable situation due to the possible complications it incurs, so that it is necessary to detect and treat it in a timely fashion. Recent evidence suggests that there is an intrauterine programming related to hyperglycemia during pregnancy, which could explain the increased risk of metabolic alterations, obesity, and diabetes among the offspring of mothers who had a pregnancy associated with diabetes [7]. Epertise by health personnel who care pregnant women is essential primordial, and is fundamental for reducing maternal and fetal morbimortality in the pregnant diabetic. It is of vital importance to identify, from the first level of care, patients with risk factors and to implement strategies that include pre-conception and dietary counseling, promoting lifestyle changes that combat a sedentary lifestyle, and timely medical intervention with the various alternatives available [8]. Luckily the current panorama for the gestating individual has improved dramatically, since in the past a pregnant woman with diabetes was inconceivable. The dis-

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covery of insulin in 1921 by the investigators Banting, MacLeod and Bets from the University of Toronto radically changed the prognosis for those ill with diabetes, as well as for gestating diabetes. Likewise, the use of glyburide and metformin during pregnancy, accepted in recent years, is one more tool in the treatment of pregestational and gestational diabetes. However, the pregnant woman with diabetes is exposed to high obstetric risk and elevated perinatal morbimortality, so it has not ceased to be a health problem.

Classification and Diagnosis

For many years, GD has been defined as an alteration in glucose metabolism, first recognized during pregnancy. In the 2016 publication of the American Diabetes Association (ADA), diabetes is classified in four general categories [9, 10]. This new classification, in contrast to the old classification by White, has greater clinical usefulness, since it is concrete, easy to remember, and applicable to diabetes during pregnancy.

1. Type 1 diabetes (T1D) which is secondary to the destruction of the beta cells of the pancreas, and in general leads to absolute insulin deficiency.
2. Type 2 diabetes (T2D) due to a progressive loss of insulin secretion.
3. GD, which is diabetes diagnosed in the second or third trimester of pregnancy and which is clearly not a previously manifested diabetes.
4. Specific diabetes, which is due to other causes, such as monogenic diabetes syndrome (such as the neonatal appearance and that in Young adults—MODY), diseases of the exocrine pancreas (like cystic fibrosis), and diabetes induced by chemical products (use of glucocorticoids after transplant or drugs for treating HIV/AIDS).

In this category, it is given as fact that both T1D and T2D may be pre-existing or pre-established in pregnancy, and that in both types there may or may not be vascular complications such as chronic hypertension, retinopathy, or nephropathy.

GD carries risks for the mother and neonate, and these risks increase with the levels of maternal glycemia after the period of pre-conception and throughout the pregnancy. GD is diagnosed based on the general criteria of the World Health Organization (WHO) of plasma glucose, or better the fasting plasma glucose and plasma glucose 2 h postprandial, or with the glucose tolerance test after ingesting 75 g of glucose orally or with the criteria of glycosylated hemoglobin (Table 65.1).

Fasting is understood as null consumption of foods for a period of 8 h; the glucose intolerance test is performed with 75 g of anhydrous glucose dissolved in water. In regard to the determination of A1c, it is worth noting that it requires standardized methods and certification for this determination.

Table 65.1 WHO criteria for diagnosing diabetes

Criteria	
Fasting plasma glucose	Equal or greater than 126 mg/dL (7.0 mmol/L)
Plasma glucose 2 h postprandial	Equal or greater than 200 mg/dL (11.1 mmol/L)
Glycosylated hemoglobin (A1c)	Equal or greater than 6.5% (48 mmol/L)
Random plasma glucose	Equal or greater than 200 mg/dL (11.1 mmol/L)

The ADA recommends a selective screening in the first prenatal visit, where the patient risk of developing GD is stratified. The risk criteria are the following: over 25 years of age, weight above normal, first-degree family history of diabetes, background of glucose tolerance disorders, background of adverse obstetric events such as stillbirths, premature or macrosomic birth, and belonging to racial-ethnic groups at high risk for diabetes (Hispano-Americans). Patients with high risk should submit to an oral glucose tolerance test. In case of not agreeing with the diagnosis at that time, the test should be repeated between 24 and 28 weeks of gestation.

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study in 2008 showed evidence that the increase in just one standard deviation in fasting glucose and 2-h postprandial levels is associated with a higher risk of birth weight above the 90 percentile, cesarean birth, neonatal hypoglycemia, blood levels of C-peptide above the 90 percentile (related to fetal hyperinsulinemia and neonatal hypoglycemia), birth before 37 weeks, shoulder dystocia or damage to the newborn, requiring intensive neonatal care, hyperbilirubinemia, and preeclampsia [11]. Consequently, after the International Association of Diabetes in Pregnancy Study Groups (IADPSG 2010) and the American Diabetes Association (ADA), proposed reducing the parameters in plasma glucose levels for the diagnosis of diabetes and a universal screening where in the first prenatal evaluation baseline glucose, glycosylated hemoglobin or casual glycemia should be determined for early detection of diabetes not recognized previously, and to start treatment and follow-up as done with previously recognized diabetes (Tables 65.2 and 65.3). It should be mentioned that ADA and the American College of Obstetricians and Gynecologists (ACOG) support the two-step strategy proposed by the National Institutes of Health (NIH) in 2013, which consists of performing a first glucose tolerance test with 50 g and in positive cases a second test with 100 g of oral glucose.

Despite differences regarding glucose levels, these diagnostic approaches have been accepted to establish the diagnosis of gestational diabetes. The results of meta-analysis comparing diagnostic criteria show similar associations in both systems, but it is evident that with the IADPSG

Table 65.2 IADPSG 2010 criteria for GD diagnosis during a glucose tolerance test with 75 g of glucose anhydrate dissolved in water

Baseline or fasting glucose	≥92 mg/dL (5.1 mmol/L)
First hour glucose	≥180 mg/dL (10.0 mmol/L)
Glucose at 2 h	≥153 mg/dL (8.5 mmol/L)

One or more of these values should be equal or greater to establish the diagnosis of diabetes

Table 65.3 Two-step strategy for the diagnosis of GD

Step 1. Perform the glucose tolerance test between weeks 24 and 28 of gestation with 50 g, without considering fasting, with determination of glucose at 1 h, in women not previously diagnosed with diabetes
1 h ≥140 mg/dL[a] (7.8 mmol/L), proceed to glucose tolerance curve with 100 g of glucose
Step 2. Glucose tolerance curve considering fasting, with 100 g of glucose and determinations of the first, second, and third hour
Fasting 95–105 mg/dL (5.3–5.8 mmol/L)
1 h 180–190 mg/dL (10.0–10.6 mmol/L)
2 h 155–165 mg/dL (8.6–9.2 mmol/L)
3 h 140–145 mg/dL (7.8–8.0 mmol/L)
The diagnosis is established when at least two of the four values are equal or greater

[a]The ACOG recommends levels below 135 mg/dL (7.5 mmol/L) in populations ethnically at high risk for GD; some experts recommend values of at least 130 mg/dL (7.2 mmol/L)

criteria, more patients are diagnosed with GD, which may lead to over-diagnosis and overtreatment. Putting the differences to one side, we do not adhere to the recommendations of ADA and IADPSG 2010, where it is established that every patient receiving prenatal care should be screened from the first prenatal visit for diabetes, preferably during the first trimester of gestation, since patients at low risk of developing GD represent barely a low percentage of the population and repeating the plasma glucose test between weeks 24 and 28 if the diagnosis is not established previously [12–14]. It is obvious that its practice will have a benefit in results that favor the pregnant woman.

Recommendations for the Diagnosis of Diabetes in the Pregnant Woman (American Diabetes Association, 2016)

1. Perform on every pregnant woman in her first visit for prenatal control a determination of fasting glucose using the standard diagnostic criteria, above all in pregnancies with risk factors in which there is not a previous diagnosis of T2D.
2. Test for a diagnosis of diabetes between weeks 24 and 28 of gestation in pregnant women not known to have previous diabetes.
3. Screening with a glucose tolerance test between weeks 6 and 12 post-partum for all women who had GD, with the object of detecting persistence of hyperglycemia and establishment of T2D.
4. Women with background of GD should have a permanent follow-up for developing diabetes or pre-diabetes at least every 3 years, since it is estimated that a considerable percentage (15–50%) of women that suffer GD develop T2D in a period of no more than 10 years.
5. All women with established history of GD or a pre-diabetic condition should receive interventions to change lifestyle or to use of metformin to prevent or delaying the development of diabetes.

Changes in Carbohydrate Metabolism in the Pregnant Woman

The metabolic changes natural in pregnancy have the object of creating an environment that allows embryogenesis, the growth of the fetus, its maturity and survival. In a normal pregnancy, directly or indirectly, the growth of the fetal placental unit increases levels of cortisol, growth hormone, human placental lactogens, estrogens, progesterone, and prolactin. In the first week of gestation, the increase in the production of estrogens and progesterone produces hyperplasia of the β cells of the pancreas, followed by an increase in the production of insulin and increased tissue sensitivity to same. This anabolism is translated into an increase in the response to insulin, which leads to fasting hypoglycemia, increased plasma lipids, hypoaminoacidemia, and a marked sensitivity to starvation. During the second half of pregnancy (particularly weeks 24–28), carbohydrate metabolism is affected by the increased production of human placental chorion gonadotropin, tumor necrosis factor α, prolactin, cortisol, and glucagon. These changes contribute to improved glucose tolerance, greater insulin resistance, reduced reserves of hepatic glycogen, and increased hepatic glycogenesis. As the gestation progresses, this response comes to be inadequate and insulin resistance is presented, which promotes a lipolysis and fasting ketonemia, as well as postprandial hyperglycemia, in which there is a greater supply of nutrients for the fetus. Placental transport of glucose is carried out through facilitated diffusion, so that maternal serum levels determine fetal levels; in a pregnancy with diabetes there is elevated fetal insulin, promoting the growth of same with increased fatty tissue and increased reserves of hepatic glycogen, which is associated with macrosomia, lipogenesis, organomegaly, polyhydramnios, etc. [15, 16]. Recently, there has been talk of leptin, which is a hormone produced mainly by fatty tissue cells, and its circulating levels are proportionate to adipose tissue mass; in the second and third

trimesters of pregnancy its levels increase substantially; its role is related to mitogenic and angiogenic processes, in the regulation of immune response and in the transportation of nutrients, all important processes during placentation and embryonic development [17].

Treatment

The handling of diabetes should comprise a preventive focus in all senses; that is why it is determinant that all women of reproductive age have access to health services, information regarding reproductive health, a family planning method, methods to prevent sexually transmitted diseases, and that they are informed of the risk a pregnancy implies in association with overweight and obesity, nutritional advice during pregnancy, and the promotion of breastfeeding since abandoning this practice increases the risk of maternal overweight and obesity. Weight gain during pregnancy should be inversely proportional to the body mass index (BMI) previous to the pregnancy, so the intervention of nutritionists and dieticians is recommended in nutritional advice to achieve objectives regarding expected weight gain during pregnancy (Table 65.4).

In patients with pregestational diabetes, it is of vital importance that the pregnancy occurs in a euglycemic environment to avoid fetal complications that accompany periconception hyperglycemia, congenital malformations, and miscarriages being frequent. In the patient that debuts with diabetes in pregnancy, education regarding self-monitoring of glucose and the presence of ketonuria is primordial, as well as educating families in the identification of hypoglycemia data. Opportune treatment of GD will significantly reduce perinatal complications such as fetal death, congenital malformations, fetal macrosomia, shoulder dystocia, bone fractures secondary to obstetric trauma, nerve lesions, and newborns with delayed intrauterine growth; it will even be a factor that will influence the future reduction in risk of juvenile obesity in the children of mothers with diabetes. The main objective in treatment is the strict control of blood glucose levels; Table 65.5 lists the main care to which every patient with pre-existing diabetes should have access. It is worth mentioning that if the healthcare model is applied by levels, the first contact doctors are in charge of detecting those patients of reproductive age with risk factors, especially patients with pre-existing diabetes (T1D or T2D) susceptible to getting pregnant, so the pregnancy is in conditions of metabolic control, and they are referred timely to second or third level care for its management.

Table 65.4 Expected weight gain during pregnancy in relation to BMI

Total gain at the end of pregnancy	BMI
12–18 kg (28–40 lb)	<18.5
11.5–16 kg (25–35 lb)	18.5–25
6.8–11 kg (15–25 lb)	25–30
5–9 kg (11–20 lb)	>30

In countries like Mexico, it has been established that women represent an intermediate-risk group from an ethnic point of view, for developing diabetes, and therapeutic goals have been established for the treatment of GD, recommended in national Clinical Practice Guides—Guías de Práctica Clínica 2009 (GPC 2009), where the objective is to achieve blood glucose levels described in Table 65.6. The implementation of the GPC in recent years in Mexico has the goal of unifying medical criteria in the diagnosis and treatment of various pathologies.

ADA, in its publication in 2016 [18], proposes the following general recommendations for the management of patients with diabetes:

1. Offer pre-conception advice that covers the importance of glycemia control as normally and safely as possible; ideally A1c should be <6.5% with the object of reducing the risk of congenital anomalies. For the area of pregnancy in the peri-conception period and an adequate prenatal control, the gynecologist and obstetrician should recommend to the woman with pregestational type 1 and type 2 diabetes, fasting glucose levels ≤90 mg/dL (5.0 mmol/L), in the first postprandial hour ≤130–140 mg/dL (7.2–7.8 mmol/L), and at 2 h postprandial ≤120 mg/dL (6.7 mmol/L).
2. Family planning is an obligatory subject, prescribing a safe, efficient anti-conceptive method until the woman is prepared and ready to be pregnant.

Table 65.5 Pregestational and antenatal care in women with pre-existing diabetes

Pregestational
Prophylactic folic acid 3–5 mg a day
Optimization of glucose levels
Retina examination
Urine examination in search of albuminuria
Blood pressure control in the case of hypertension
Advice regarding the increase in the incidence of fetal morphological malformations and increase in the risk of severe hypoglycemia events during the first trimester of gestation
Antenatal
Adequate glucose control during pregnancy
Advice for optimum weight gain during the pregnancy, based on the mother's body mass index
Ultrasound examination in search of fetal malformations between weeks 12 and 14 and around 20 weeks
Evaluation of fetal growth (cephalic and abdominal circumference) every 4 weeks after 20 weeks and every 2 weeks after 28 weeks. Determinations of amniotic fluid
Advice on the incidence of fetal movement (perceived by the mother)
Determination of the time and birth type based on gestational age, glucose control, and estimated fetal weight

Table 65.6 Therapeutic goals in the management of GD in Mexico

Fasting glucose	60–90 mg/dL (3.3–5 mmol/L)
1 h postprandial	≤140 mg/dL (7.7 mmol/L)
2 h postprandial	≤120 mg/dL (6.6 mmol/L)
If fetal growth is equal to or greater than the 90 percentile, glycemia goals will be more strict:	
Fasting	≤80 mg/dL (4.4 mmol/L)
2 h postprandial	≤110 mg/dL (6.1 mmol/L)

Table 65.7 Dietary portions in relation to the body mass index (BMI)

Caloric portion	BMI
36–40 kcal/kg of current weight	<19.8
30 kcal/kg of current weight	19.8–26
24 kcal/kg of current weight	26–29
And should be personalized	>29

Of the total kilocalories, 40 m to 45% should correspond to carbohydrates, 20–25% proteins, and 40% or less fats, of which less than 10% should be saturated fats

3. Women with pre-existing type 1 or type 2 diabetes who plan to get pregnant or are pregnant should be advised of the risk of developing and/or the progression of diabetic retinopathy. Vision examinations before the pregnancy or in the first trimester of gestation, then every trimester, every year after the birth, and as suggested by the specialist according to the degree of retinopathy.
4. Change in lifestyle is an essential component in the management of GD and can be the first pattern for treatment.
5. Medications should be added if necessary with the goal of reaching glycemic objectives. The pharmaceuticals broadly accepted in GD are insulin and metformin; glyburide can be used, but it has a higher rate of neonatal hypoglycemia and macrosomia compared with insulin or metformin. Other agents have not been adequately studied. The majority of the oral agents cross the placenta, and all lack long-term safety data.
6. The change in lifestyle means reducing to a minimum the sedentary lifestyle and promoting adequate diet. It is of vital importance to have nutritional counseling for the patient with pre-existing diabetes or diabetes which is manifested during pregnancy, since in the majority of cases it can be sufficient to reach adequate control of glucose levels. Nutritional counseling is not exclusive to a nutritionist, since from the first office visit the doctor or prenatal nurse can orient the pregnant patient, whether or not she has diabetes. And when conditions allow it, every pregnant patient with diabetes or risk factors should be referred to a nutritionist. The recommended dietary portions are the following (Table 65.7).

Insulin

Insulin does not cross the placental barrier and has been, for many decades, the basis of treatment for glycemic control in pregnant women, and it has the consensus of various international organizations such as the American College of Obstetricians and Gynecologists (ACGO), the American Diabetes Association (ADA), and the Food and Drug Administration (FDA). It is the pharmacological intervention of first choice in GD, accepted by various organizations and countries. The insulins approved for use during pregnancy are immediate and rapid (INPH and IR), along with short-action analogues such as lispro and aspart. Not approved for use during pregnancy are long-term insulin analogues such as glargine and determir. Insulin schema may be somewhat complex to indicate to the patient, and the success of their administration depends on various factors, among them the ability of the patient and skill given before application. The total dose may vary from patient to patient, which is calculated by kilo of weight per day; if the patient is thin 0.1–0.3 IU per kilo of weight per day is considered, and if obese 0.4–0.7 IU per kilo of weight per day. At the start of pharmacotherapy, it is important to start with lower dosage, in order to avoid unexpected hypoglycemia. One common strategy for dosing consists in dividing the total dose into two applications in which 2/3 will be applied in the morning before breakfast and 1/3 before dinner. IR is added when the therapeutic goal of postprandial glycemia is not reached, in which case the morning 2/3 dose would be INPH and 1/3 rapid action, and at dinner it would be ½ INPH and ½ rapid action. This schema can be adjusted with dosage up to 1.5 IU/Kg of weight/day, according to the evolution of the patient and the time of gestation, since in the second and third trimester a greater need for insulin is expected due to the resistance found in this stage of pregnancy [19].

The Use of Oral Hypoglycemic Drugs in Pregnancy

In the United States, oral hypoglycemic drugs have not been specifically approved by the FDA for treatment in GD. However, in the last decade there has been growing scientific evidence in favor of oral hypoglycemic drugs, which, compared with insulin, have the advantage of not requiring multiple injections and therefore fewer events of hypoglycemia, as well as a lower cost. Their use during pregnancy is increasing, above all in women with GD and pre-existing T2D, and especially in women with excess weight. Glyburide and metformin are within group B of the FDA as medications for use during pregnancy. This means that reproduction studies in animals have not demonstrated risks to the fetus. There are no studies in pregnancies, but their use has been

approved in pregnancy. Before prescribing any oral hypoglycemic drugs, one should remember that they cross the fetal placental barrier and, although no adverse effects to the fetus have been reported, long-term studies are scarce. Therefore, we will concentrate on the details of only two oral antidiabetics: glyburide and metformin.

Glyburide

Glyburide is a potent anti-diabetic agent belonging to the second generation of sulfonylureas and also known as glybenclamide. Its hypoglycemic drugs action is due to stimulation of beta cells in the pancreatic islets that cause an increase in the secretion of insulin. Also considered a secretagogue, it is absorbed orally and does not depend on food; it is metabolized in the liver and reaches maximum concentrations in approximately 3 h, with a half-life of 8 h. Sulfonylureas join the receptors in the ATP-dependent potassium channels, reducing the passage of potassium and producing depolarization of the membrane. This depolarization stimulates the entry of calcium through the calcium channels, increasing intracellular calcium concentrations, which in turn induces the secretion and/or exocytosis of insulin. For this drug to be effective, it requires a minimum number of viable beta cells. Prolonged administration of glyburide also causes extra-pancreatic effects that contribute to its hypoglycemic drugs activity, such as reduction of hepatic glucose production and improved insulin sensitivity in peripheral tissues, the latter due to an increase in the number of insulin receptors and more efficient union of insulin with its receptor. Glyburide reduces the circulating levels of glucose by 20% and is most efficient in patients with normal weight or slight overweight. It was the first oral hypoglycemic drugs tested and used prospectively to manage GD, and its effectiveness is similar to insulin. In comparison with insulin, it is less likely to experience maternal hypoglycemia, and only 1–15% experience symptomatic hypoglycemia. The most common side effects are at the gastrointestinal level, and include slight nausea, epigastric burning, or the sensation of fullness; dermatological ones such as a slight itch or rash and increasement in hepatic function tests that are rarely associated with icterus. The current recommended dosage is 2.5–5 mg a day or twice a day, with a maximum dose of 20 mg. Its use is not recommended if the patient is lactating, although this is not an indication for suspending lactation since lactation at the maternal breast has many benefits for both fetus and mother [20].

Metformin

This is a biguanide that has the effect of reducing insulin sensitivity. Like glyburide, metformin and other biguanides require residual function of the pancreatic β cells in order to be effective. It reduces fasting and postprandial glucose. It acts through three mechanisms: (1) it reduces hepatic production of glucose by inhibiting gluconeogenesis and glycogenolysis, (2) in muscle it increases insulin sensitivity and improves the capture of peripheral glucose, as well as its use, and (3) it delays intestinal absorption of glucose. It does not stimulate insulin secretion, so it does not provoke hypoglycemia. It is used alone or in combination with glybenclamide or with insulin. The dose is 1000–2000 mg a day, divided into two doses with food or after it. The commonly reported side effects are nausea, vomiting, and increase in intestinal movement. Its widespread use in women with pregestational diabetes, with polycystic ovary syndrome and low fertility, marked the pattern for its use in pregnant patient with diabetes. When metformin use continued into the end of the third trimester, no side effects were observed to mother or fetus associated with its consumption. Recent studies have evaluated glycemic control in women with GD treated with metformin vs. insulin and have demonstrated that metformin is an effective agent for adequate glycemic control; it was also observed that women treated with metformin have less weight gain during pregnancy [21]. Meta-analysis studies have established that metformin has efficacy and safety similar to insulin in terms of neonatal hypoglycemia; the frequency of products with higher weight for gestational age, newborn entry into phototherapy, respiratory stress syndrome, and perinatal death. Metformin is safe in regard to incidence of peaks in hypoglycemia. However, it is necessary to state that there is a need for additional studies, with greater sample sizes that evaluate the long-term effect on children born to women with GD treated with metformin [22, 23]. Metformin is excreted in human mother's milk. No adverse effects have been observed in newborns or breastfed babies. However, as there is only limited data available, breastfeeding is not recommended during treatment with metformin. Each individual case should be decided as to interruption of breastfeeding, taking into account that the benefits of maternal breastfeeding are greater compared with the potential risk of adverse effects in the breastfed.

Management of Pregnancy

To date there is no consensus regarding how to solve pregnancy of the patient with diabetes, and most is based on recommendations and points of good practice. Every patient with GD should be referred for its control and treatment from the moment this diagnosis is known, to a second or third level hospital that has a multidisciplinary team that includes the services of obstetrics, perinatology, endocrinology, nutrition and diet, social work, psychology, etc. Structural ultrasound should be performed between weeks 18 and 22, to discard

fetal malformations, and series of ultrasounds every 4 weeks with measurement of fetal abdominal perimeter at the start of the third trimester to identify fetuses with greater risk of macrosomia. At week 32 of gestation cardiotocographic tests should start without stress once a week and increase to twice a week from week 36. There should be evaluations by ultrasound of amniotic fluid levels, estimated weight, and fetal abdominal perimeter. There is no evidence-based medication regarding the decision to induce labor or keep waiting, but this is a decision that worries the obstetrician since in these patients there is a higher rate of intrauterine fetal death and higher risk of shoulder dystocia associated with fetal macrosomia. In addition, the fetus may have greater weight for gestational age, situation that can cause confusion at the time of deciding the time for interruption and conditions a premature birth that has hyaline membrane and respiratory stress. These patients have four times more mortality compared with nondiabetic pregnancy. Scheduling the birth by cesarean to avoid obstetric trauma is normally offered to patients with GD in order to prevent cases of obstetric trauma in newborns with macrosomia. Induced labor at term may have a success rate of 80%, but with a significantly higher rate of cesareans compared with uncomplicated pregnancies. Studies recommend the induction of labor at 39 weeks of gestation for women with glucose levels controlled with insulin or oral hypoglycemic drugs [24, 25]. During labor in patients with pre-existing or gestational diabetes, glucose levels should be monitored and maintained at a range between 70 and 110 mg/dL (3.6–6.1 mm/L), ranges that are recommended by ACOG and the American College of Endocrinology (ACE) [26], since high levels of glucose during labor have been associated with a greater risk of neonatal hypoglycemia. Achieving this goal requires glucose intravenous solutions and continuous insulin infusions or else rapid action insulin previous to capillary glucose medication. The demands for glucose as a source of energy increase during labor, contrary to the many institutions that restrict caloric consumption due to the risk of maternal aspiration. Women with T1D require glucose supplements to maintain adequate blood values in order to reduce cetoacidosis. Women with T2D and GD may have sufficient reserves of glycogen to maintain glucose levels around 70 mg/dL, during the latent phase of labor, without the need for glucose supplementation. However, glucose requirements increase during the prolonged induction of labor, active labor, and during the expulsion phase. Neonate should be monitored regarding hypoglycemia, hypocalcemia, and hyperbilirubinemia. In the post-labor phase, women should be able to restart normal diet. After birth, the hyperglycemic effects of placental hormones quickly disappear and plasma glucose levels return to normal, but it is recommended to test glucose concentrations for the first 24–72 h with capillary glucose to exclude persistent hyperglycemia in the post-birth period. Women with a background of GD should have follow-up for the next 6–12 weeks' post-birth with a glucose tolerance test to discard diabetes or carbohydrate intolerance, since it is estimated that 70% of these women have a risk of developing T2D up to 10 years later [27]. Maternal breastfeeding alone the first 6 months and complementary until 2 years offers benefits that prolong the effects of intrauterine hyperglycemic environment in newborns and infants of mothers with obesity or diabetes; likewise, it has benefits in maternal glucose metabolism that prevents or delays the establishment of metabolic syndrome or T2D [28, 29].

Conclusions

Women in whom GD is diagnosed should be treated with nutrition therapy and, when necessary, medication for both fetal and maternal benefit. Insulin and oral antidiabetics have equivalent in efficacy, and either can be an appropriate first-line therapy in GD. During the first trimester of gestation all pregnant women should be screened for GD, whether by the patients medical history, clinical risk factors, or laboratory screening test results to determine blood glucose levels. Women with GD should be counseled regarding the option of scheduled cesarean delivery when the estimated fetal weight is 4500 g or more. Women with GD with good glycemic control and no other complications can be managed expectantly. In most cases, women with good glycemic control who are receiving medical therapy do not require delivery before 39 weeks of gestation. Postpartum screening at 6–12 weeks is recommended for all women who had GD to identify women with T2D, impaired fasting glucose, or glucose tolerance test repeat testing at least every 3 years.

Multiple-Choice Questions

1. Gestational diabetes is defined as:
   (a) The lipid metabolism disorder during all of pregnancy.
   (b) **Carbohydrate metabolism alteration first diagnosed in the second or third trimester of gestation.**
   (c) Amino acid metabolism alteration after the second half of pregnancy.
   (d) Carbohydrate metabolism alteration first diagnosed in the first or second trimester of gestation.
   (e) Carbohydrate metabolism alteration first diagnosed in the third trimester of gestation.
2. The growing index of obesity is a global problem; bad dietary habits and sedentary lifestyle are the main factors unleashing the development of GD.
   (a) False.
   (b) **True.**
   (c) Only obesity is a factor.

(d) Only bad dietary habits.
(e) Only a sedentary lifestyle.

3. What percentage of pregnancies are complicated by diabetes?
   (a) **6–7%**
   (b) 50%
   (c) 1%
   (d) 90%
   (e) 20%
4. In GD, it is known that there is a risk factor related to ethnicity. Which populations are most susceptible to suffering GD?
   (a) **Hispanics, Afro-Americans, Native Americans, Asians and Pacific Islanders.**
   (b) Nordics and Africans.
   (c) Asians, French and Russians.
   (d) Muslims.
5. The following is true in regard to the classification of diabetes, as published by ADA 2016.
   (a) Type 1 diabetes (T1D) is secondary to the destruction of the beta cells of the pancreas and leads to absolute insulin deficiency.
   (b) Type 2 diabetes (T2D) is due to a progressive loss of insulin secretion.
   (c) GD is diabetes diagnosed in the second or third trimester of pregnancy which is not a clearly manifested diabetes.
   (d) Specific diabetes is due to other causes, such as monogenic diabetes syndrome (such as neonatal appearance diabetes and in youths—MODY), diseases of exocrine pancreas (such as cystic fibrosis), and diabetes induced by chemical products (use of glucocorticoids after transplant or drugs for HIV/AIDS).
   (e) **All of the above.**
6. Are risk factors for developing GD?
   (a) Age under 25 years, weight below normal, family history of breast cancer.
   (b) Age over 35 years, history of stillbirth and sterility.
   (c) **Age over 25 years, weight above normal, first-degree family history of diabetes, background of glucose intolerance, history of adverse obstetric events such as stillbirth, prematurity or macrosomies and belonging to ethno-racial groups at high risk for diabetes (Hispano-Americans).**
   (d) Background of previous pregnancies with fetal microsomia.
   (e) Background of previous births with intrauterine death.
7. What percentage of women that suffer GD develop type 2 diabetes in a lapse of no more than 10 years?
   (a) **15–50%**
   (b) 1%
   (c) 0%
   (d) 100%
   (e) 3%
8. Diagnosis criteria for GD during a glucose tolerance test with 75 g of glucose dissolved in water of the IADPSG 2010:
   (a) Fasting glucose equal or greater than 200 mg/dL (5.1 mmol/L), glucose at the first hour equal or greater than 180 mg/dL (10.0 mmol/L), glucose at 2 h equal or greater than 153 mg/dL (8.5 mmol/L), one or more of these values to establish diagnosis.
   (b) **Fasting glucose equal or greater than 92 mg/dL (5.1 mmol/L), glucose at 1 h equal or greater than 180 mg/dL (10.0 mmol/L), glucose at 2 h equal or greater than 153 mg/dL (8.5 mmol/L), one or more of these values to establish the diagnosis.**
   (c) Fasting glucose equal or greater than 300 mg/dL (5.1 mmol/L), glucose at 1 h equal or greater than 180 mg/dL (10.0 mmol/L), glucose at 2 h equal or greater than 153 mg/dL (8.5 mmol/L), one or more of these values to establish diagnosis.
   (d) Fasting glucose equal or greater than 400 mg/dL (5.1 mmol/L), glucose at 1 h equal or greater than 180 mg/dL (10.0 mmol/L), glucose at 2 h equal or greater than 153 mg/dL (8.5 mmol/L), one or more of these values to establish diagnosis.
   (e) Fasting glucose equal or greater than 500 mg/dL (5.1 mmol/L), glucose at 1 h equal or greater than 180 mg/dL (10.0 mmol/L), glucose at 2 h equal or greater than 153 mg/dL (8.5 mmol/L), one or more of these values to establish diagnosis.
9. The insulin dose for GD is:
   (a) **The total dose may vary from patient to patient, which is calculated for kilo of weight per day; if the patient is thin use 0.1–0.3 IU per kilo of weight per day and if obese, 0.4–0.7 IU per kilo of weight per day.**
   (b) The total dose may vary from patient to patient, which is calculated for kilo of weight per day; if the patient is thin use 1–2 IU per kilo of weight per day and if obese, 0.4–0.7 IU per kilo of weight per day.
   (c) The total dose may vary from patient to patient, which is calculated for kilo of weight per day; if the patient is thin use 0.1–0.3 IU per kilo of weight per day and if obese, 1–2 IU per kilo of weight per day.
   (d) The total dose may vary from patient to patient, which is calculated for kilo of weight per day; if the patient is thin use 3 IU per kilo of weight per day and if obese, 4 IU per kilo of weight per day.
   (e) The total dose may vary from patient to patient, which is calculated for kilo of weight per day; if the patient is thin use 5 IU per kilo of weight per day and if obese, 3 IU per kilo of weight per day.

10. Of oral hypoglycemic drugs, the following is false:
    (a) In the last decade, there is growing scientific evidence in favor of oral hypoglycemic drugs to manage GD, which in comparison with insulin have the advantage of not requiring multiple injections; there are fewer events of hypoglycemia and the cost is lower.
    (b) Glyburide is a potent anti-diabetic agent belonging to a second generation of sulfonylureas and also known as glybenclamide. It is a biguanide that reduces insulin sensitivity.
    (c) Like glyburide, metformin and other biguanides require residual function of the beta cells of the pancreas to be effective in managing GD and T2D.
    (d) The current recommended dose of glyburide is 2.5–5 mg a day or twice a day, with a maximum dose of 20 mg. The recommended dose of metformin is 1000–2000 mg a day, divided into two doses with food or after same.
    (e) **No oral hypoglycemic drugs should be used in treating GD.**

Glossary

ACOG The American College of Obstetricians and Gynecologists.

ADA The American Diabetes Association.

BMI is the result of dividing the weight of a person in kilograms by the square of his height in meters.

Congenital malformations are anatomic alterations that occur in the intrauterine stage and may be alterations in organs, extremities, or systems, due to environmental, genetic factors, deficiencies in nutrient capture, or consumption of noxious substances.

ENSANUT 2012 National health and nutrition survey 2012 (Mexico).

FDA The Food and Drug Administration.

Fetal macrosomia Traditionally, fetal macrosomia has been defined as arbitrary weight at birth, such as 4000, 4100, 4500, or 4536 g. It is currently defined as a fetus that is large for gestational age (>90 percentile).

GD Gestational diabetes, which is defined as alteration in carbohydrate metabolism diagnosed for the first time in the second or third trimester of gestation.

HAPO Study Hyperglycemia and Adverse Pregnancy Outcomes study.

IADPSG The International Association of Diabetes in Pregnancy Study Groups.

Insulin From the Latin "isla." It is a polypeptide hormone formed by 51 amino acids, produced and secreted by the beta cells of the Isles of Langerhans of the pancreas. Discovered by Frederick Grant Banting, Charles Best, James Collip, and J.J.R. Macleod of the University of Toronto, Canada, in 1921.

NIH National Institutes of Health.

Obesity Obesity and overweight are defined as abnormal or excessive accumulation of fat that may prejudice health. A simple way to measure obesity is the body mass index (BMI), which is the weight of a person divided by height in meters squared. A person with BMI equal or above 30 is considered obese and with a BMI equal or greater than 25 is considered overweight.

Oral hypoglycemic drugs Anti-diabetes drugs which are classified as sulfonylureas, biguanides, alpha-glucosidase inhibitors, meglytinids (Repaglinide, Nateglinide), and thiazolidinediones.

Perinatal mortality is the fetus and newborn risk of dying as a consequence of the reproductive process.

Premature birth According to WHO, birth that occurs after week 20 and before 37 complete weeks.

T1D Type 1 diabetes, which is secondary to the destruction of the beta cells of the pancreas, and in general leads to absolute insulin deficiency.

T2D Type 2 diabetes, which is due to a progressive loss of insulin secretion.

WHO World Health Organization.

Women of reproductive age Women between 15 and 44 years.

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The Elderly with Diabetes

66

Willy Marcos Valencia

Diabetes in Older Adults

Diabetes is chronic and progressive, with increasing prevalence in older age groups [1]. Moreover, with longer disease duration, there is greater risk to develop its complications. In parallel, aging itself increases the risk for age-related or age-dependent chronic diseases, such as cardiovascular [2], cancer [3], depression [4], dementia [5], and frailty (increased vulnerability and poor health outcomes) [6]. Ultimately, the scenario of diabetes in the older adult is more complex and complicated than in younger age groups, with heterogeneous presentations at the real clinic setting, even for subjects of the same age and similar comorbidities [7].

There will be two billion people older than 60 by the year 2050, from which 434 million will be older than 80, and about 1 out of 4 will have diabetes [8]. Therefore, we need to increase our understanding and dissemination toward better, safer, effective, and efficient approaches to this group.

To accomplish this goal, it is necessary to enhance the understanding of diabetes and aging in the older population. Figure 66.1 offers a magnified visual perspective, aiming to summarize the multiple factors that ought to be considered when evaluating an older patient with diabetes.

Geriatric Considerations in the Management of Diabetes in the Older Adult

The guidelines from the American Diabetes Association (ADA, Chap. 11) [14] provide multiple recommendations and considerations to expand the approach to diabetes especially for this age group. Notably, this approach was built upon a consensus by experts from both the ADA and the American Geriatrics Society (AGS) [15]. What might be the most valuable contribution is the framework to stratify patients according to their health status and disease burden (summarized in the form of a table), which was then adopted by the ADA guidelines.

The framework (presented as a table) provides clinicians with a practical framework how to stratify their patients, and from there, individualize targets and therapies. This approach offers a tool to disseminate the need for individualization of targets and therapies based on factors that go beyond the presence of macrovascular complications.

Nevertheless, while there can be other suggested approaches, including those for specific settings such as long-term care [16], we recommend clinicians to take advantage from this framework, especially intended to those teams without formal training in geriatrics.

The approach stratifies patients in three settings. A reasonable approach to present this information would be as follows:

The healthy older adult: As long as there are no major multiple and/or life-threatening diseases, and in the absence of functional or cognitive deficit, these older adults could potentially benefit from approaches similar to those of younger age. We recommend considering factors such as life expectancy, in addition to patient-centered discussions for preferences and feasibility of implementing escalating strategies to achieve the desired targets. As with everything in geriatrics, the principle of "start low, and go slow" will also apply in this setting. On the other hand, having such patient with uncontrolled diabetes and not providing further interventions would be consistent with clinical inertia, which can also be observed in this population.

The older adult with severely complex health scenario: This is the third situation, in which older patients are enduring multiple severe chronic diseases, with impairment in physical function (activities of daily living) and memory disorders. Many are already in long-term care, or palliative care, or are eligible for those services.

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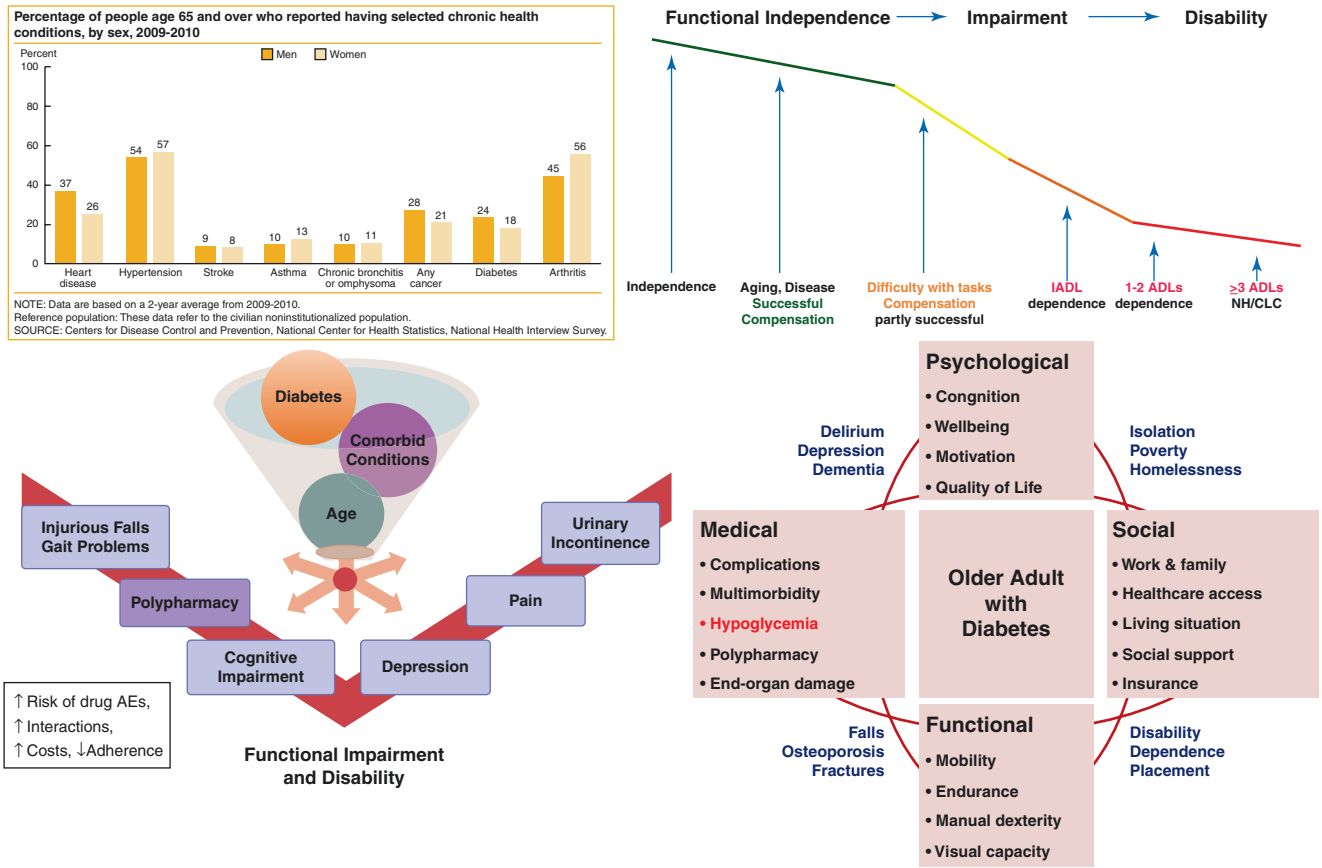

Fig. 66.1 A geriatrics approach to understanding diabetes in the older adult. On the left upper corner, the prevalence of chronic diseases increases in the older population [9]. Beyond the traditional diabetes-related complications, older adults with diabetes will also have a variety of multiple other chronic diseases, increasing their pharmacologic needs and regimens, the risk for drug-to-drug and drug-to-disease interactions. Thus, their diabetes care will start at a higher level of burden, complexity, and impact to their lives. On the right upper corner, a simplified yet powerful depiction on how function changes, and declines, throughout the lifespan of a person (slide courtesy of Hermes Florez, based on literature from Verbrugge et al. [10]). Younger patients will usually be considered as independent and able to compensate for the disease burden (granted there will be a spectrum of reactions). In this setting, providers would usually give for granted the young patients' ability to take care of themselves. On the other hand, with accumulating/worsening chronic diseases, all human beings go through an aging process that culminates with certain death. Excluding those who may suffer an acute fatal event (e.g., sudden cardiac death or accidents), the rest will go through a progressive course of functional decline (some earlier, other later). Clinicians must recognize that these processes are very heterogeneous, and for those unable to compensate, there will be a loss of the ability to carry the instrumental activities of daily living (or IADLs), which include managing medications. On the left lower corner, the additive effects of diabetes, aging, and multimorbidity can be associated with a variety of geriatric syndromes, further increasing the risk for progressive functional decline and disability (slide courtesy of Hermes Florez, based on literature from Laiteerapong et al. [11]). Hence, considering the physical/mental decline, in the setting of multiple diseases and complex regimens, the negative consequences also include greater risks for adverse complications (e.g., hypoglycemia), poor quality of life, and increased social and economic burden [12]. Finally, on the right lower corner, a previously presented visual summary of our geriatrics approach to the older adult with diabetes [7]. The four geriatric domains are intertwined, especially in the setting of this chronic disease, causing complications of its own (within the medical domain), and also interacting with the functional, mental/psychological, and social domains. The arrows go in both directions. From one side, diabetes fosters new medical issues (e.g., diabetes leading to depression leading to poor motivation and poor quality of life), and on the other direction, situations that hinder diabetes management (e.g., poor family support leading to social isolation leading to poor diabetes control). In summary, the clinical scenario of an older adult with diabetes, and multimorbidity, impaired physical and cognitive function (both a consequence from diabetes itself, or associated with age-related diseases), will have implications and consequences for diabetes self-management and self-efficacy, quality of life, and increasing vulnerability [13]. Hence, the need to implement strategies that can counter the challenges, while adjusting therapeutic targets and interventions. To do so, provider caring for older adults with diabetes will benefit from gaining insights to the "geriatrics field"

Then, the scenario in between, defined for older patients with chronic diseases but still independent, without severe physical or cognitive dysfunction, and preserved activities of daily living, but might have issues with instrumental activities of daily living (which include management of medications).

One of the most striking points from this framework is that geriatric syndromes (falls and urinary incontinence) are determinant factors and need to be incorporated in the assessment and plan. Note that clinicians need not become Geriatricians, but rather incorporate some geriatric approaches to the care of older patients with diabetes.

Geriatric Syndromes and Assessments for Older Patients with Diabetes

In order to effectively apply the framework from ADA/AGS as discussed in the prior section, we need to expand the description of geriatric syndromes and the comprehensive geriatrics assessment. Noteworthy, addressing, assessing, and incorporating these factors into the care of an older patient with diabetes will be feasible to conduct, even at a busy clinic setting.

As previously established, older age and the aging process lead to greater risk for developing chronic medical diseases, functional and cognitive decline, and then, the geriatric syndromes. These geriatric syndromes, while being syndromes, can have multifactorial etiologies, but usually share common risk factors and pathophysiologic mechanisms. Screening and detection is a key factor for management, even if the final diagnosis is not ultimately defined [17].

Considering the setting of diabetes, we can map them all to the heightened burden produced by long-standing disease, especially if complications presented. The geriatric syndromes include polypharmacy, urinary incontinence, impaired mobility, falls, frailty, persistent pain, cognitive impairment, and depression, and they add further complexity to older patient with diabetes [17–19]. Progression in these syndromes lead to poor quality of life and loss of independence, a situation where patients will require assistance to care for themselves, and even transition to institutionalization of different types (assisted living facilities, community living centers, or nursing homes).

The connection between diabetes and geriatric syndromes has been described. For example, a French study of 987 older patients (age ≥ 70) with diabetes found that both macrovascular [20] and microvascular [21] complications were associated with cognitive function, nutritional risk, and evidence for self-care deficit. The authors highlighted the multiple and potential bidirectional pathways between cardiovascular disease and geriatric syndromes.

Table 66.1 presents a distribution of geriatric syndromes within each of the four geriatric domains. This operationalization is solely for practical purposes, since in reality, there will be significant overlap (one syndrome connected to more than one domain), related to pathophysiology and outcomes.

Table 66.1 Geriatric syndromes within the four geriatric domains

Medical	Functional	Psychological	Social
Polypharmacy	Impaired mobility	Dementia	Social isolation
Multimorbidity	Falls	Depression	Homelessness
Malnutrition	Urinary incontinence	Poor quality of life	Food insecurity
	Frailty		
	Self-care deficit		

Medical Domain

Polypharmacy: There are several ways to define polypharmacy (based on the total number of medications, the number of medications for one condition and the use of medications that are not justified by benefits over risks) [22]. However, it is easy to understand how an older person with diabetes and diabetes-associated complications will likely meet the first two definitions, just by following the standard-of-care treatment [23]. The issue is that as these medications accumulate, polypharmacy leads to increased costs and non-adherence [24], and non-adherence leads to uncontrolled glycemic control. Moreover, increased economic costs lead to mental preoccupation/anxiety as well as socioeconomic burden.

Each visit is an opportunity to review the medication profile, and ensure (1) patient knowledge and justification for each medication, (2) advise against non-required over the counter, and (3) promptly adjust therapeutic interventions, striving to reduce medications when there is no certainty that the benefits outweigh the risks. Moreover, the patient can be further engaged in self-management as improvements in lifestyle could be clinically significant enough and warrant fewer medications, ultimately improving diabetes and patient-centered goals.

Unfortunately, polypharmacy will be quite prevalent in the older population with diabetes, and will often be related to other geriatric syndromes such as falls [25, 26], which will be further reviewed in a subsequent section. Additionally, a vast majority of older patients with diabetes will have an indication for an antihypertensive medication, with indications ranging from primary/secondary prevention of diabetic nephropathy in normotensive patients, all the way to established hypertension, heart disease, and others. The key factor will be to ensure the patients do not have orthostatic hypotension, and to adjust pharmacologic therapies accordingly. Most notably, these changes can greatly benefit the patient. Decreasing psychotropic agents and polypharmacy reduces the risk for falls [27, 28].

Multimorbidity: The accumulation of multiple chronic diseases is a common scenario in the older patient [29], but not always associated with non-disease-based physical limitations [30]. Hence, their presentation and impact is highly variable, leading to different health status, between individuals, and over time. Most notably, different older persons with similar conditions may present with different clinical status.

Researchers have modeled the disease clusters from 750 aging patients, and found that older patients with established cardiovascular disease and highest burden of comorbidities (≥6 per their study) will benefit less from intensive regimens [31]. From our standpoint, we agree with this concept, consistent with the different strata presented in the ADA/AGS framework, but emphasize that the "paper can be deceiving." Before meeting a new patient, most clinicians review the clinical information available in medical records, and we have found a very heterogeneous presentation of health status, beyond the records, based on physical and cognitive function. Notwithstanding, chronic medical conditions might impact daily functioning and health-related quality of life (HRQOL). Older adults with longer disease duration, or uncontrolled disease, with complications, will be at greater risk for impaired daily functioning and poor HRQOL.

Nutritional Status: While this is not a geriatric syndrome per se, we need to unveil, even if only briefly, the associated syndromes of frailty with sarcopenic obesity. Diabetes is associated with obesity as we age [32]. Many older patients with diabetes, as they age, and as they develop functional impairment due to the diabetes and its complications and other age-related problems, then remain with increased weight, but endure changes in body composition, with loss of lean mass. Obesity itself affects all four geriatric domains, and if left untreated, leads to a vicious cycle of progressive deterioration of physical activity, function, worsening of diseases, further weight gain, and further worsening of this "setting" [33]. Consequently, the success on diabetes management will be challenged by the persistence of such negative scenarios in the geriatric population.

Malnutrition

On the other hand, despite the obesity epidemic and the clear relationship between obesity, insulin resistance, and diabetes, the proportion of malnutrition risk is similar in subjects with diabetes than in others in the community [34] and in hospital [35]. In other words, older patients with obesity may suffer from macro- and micronutrient deficiency. Moreover, in connection to the aging process and concomitant chronic diseases, the risks for malnutrition are greater in this age group. It has even been shown that diabetes in stroke patients is a risk factor for malnutrition, probably due to dietary restriction and higher rate of dysphagia [36]. Thus, oral health and swallowing capacities must be checked. Particularly, oral candidiasis must be searched and treated and patient referred to dentist surgeon. Nutritional interventions and lifestyle changes need to be adapted to individualized nutritional risks.

Functional Domain

Diabetes is associated with early declines in physical function [37]. Hence, older patients with long-standing disease have been exposed to diabetes-related decline, apart from the "expected" age-related decline.

Moreover, dexterity and physical capacity are needed to perform diabetes self-management (for instance, visual loss can impair the ability to read glucose results and inject insulin units). Tools such as the insulin delivery systems, with training for those with visual impairment, can be implemented to allow the person to maintain independence in the management of diabetes.

Within this domain, we assess the geriatric syndromes of falls, impaired mobility, functional decline, vision loss, and hearing loss, which are among the most common geriatric syndromes. More recently, the frailty syndrome continues gaining increasing attention, and the future might have evidence to support that frailty ought to be included in the framework as well as falls and urinary incontinence.

Impaired Mobility

The most common risk factors are older age, low physical activity, strength or balance impairment, and chronic diseases such as obesity, diabetes, and osteoarthritis [38]. Hence, unsurprisingly, mobility impairment is common in older adults. Unfortunately, with diabetes and other diseases sharing mutual risk factors, and in itself, counters the potential for disease prevention. Clinicians need to assess and understand the impact from impaired mobility, dexterity, and function to define the most appropriate plan of care.

Self-Care Deficit and Functional Decline

The assessment of Instrumental Activities of Daily Living (IADLs) [39] explores capacities to live in an autonomous way at home. These activities include shopping, cooking, household cleaning/laundry, telephone use, managing medications, finances, and driving/using public transportation. The inability to carry at least two or more IADLs would place a patient in the second category from the ADA guidelines. Nevertheless, limitations on these IADLs can be supplemented through informal (family/friends) or formal support (e.g., home health nurse to assist with medication management). The assessment of Activities of Daily Living (ADLs) [40] explores the actions to take care of basic needs without help. These include dressing, toileting, bathing, eating, and getting around the home. Limitations in two or more ADLs are consistent with the highest complexity in the ADA

model, and glycemic targets are further increased. These limitations are also consistent with nursing home level of care. However, again, these limitations can be supplemented by formal or informal support, with the main objective to keep the patient at home. Often, structural modifications are helpful.

The dependency in IADLs is mainly associated with cognitive troubles. Particular attention should be given to the capacities to self-manage medications. Care plan can be adjusted based on the outcomes from this assessment. Sensory loss, particularly but not only visual loss, can impact diabetes self-management and self-efficacy. When detected, referral to specialist and subsequent intervention may facilitate the management of diabetes in the older person.

Falls

Due to the strong connection between diabetes and falls, we decided to expand this section. Falls are generally driven by a combination of intrinsic (the person's characteristics) and extrinsic (exogenous, the environment) factors. Falls risk is already increased by age (without diabetes), due to age-related decline in gait, balance, proprioception, and sarcopenia [41, 42]. In addition, there are multiple mechanisms by which diabetes and its complications increase the risk for falls. Diabetes can contribute in several ways to the intrinsic factors, impairing gait (diabetic peripheral polyneuropathy, diabetic peripheral vascular disease and amputations, neuropathic pain), vision (diabetic retinopathy), judgment (dementia in diabetes), balance (autonomic dysfunction), and the combination of impaired judgment and balance (pharmacotherapy and hypoglycemia) [43–47]. Ultimately, the combination of older age and diabetes increases falls risk by 17-fold [42, 48], while the involved diabetes-related factors will have an additive effect and worsen this risk [49].

Falls are terribly under-detected, and it is imperative to understand its definition. A true fall is defined as a person coming to rest inadvertently on a level below their prior location [50]. Falling from a standing position to the ground is not the only scenario. An older patient might try to go from supine to sitting and from sitting to standing, and they might go back to supine or sitting, respectively, and these will qualify as falls too. Even without considering those scenarios (which are severely under-detected) "traditional" falls are more prevalent in older people, and this is the age group at the greatest risk for serious injury or even death [51], constituting a public health problem that is largely preventable [52]. Unfortunately, less than half of providers know that their patients are falling [53]. Furthermore, the quality of bone in diabetes is affected, making them more vulnerable for fragility fractures [54]. Patients receiving insulin therapy are at greater risk for falls (requiring hospitalization) compared to those without diabetes [55]. Additionally, a fall can be the presentation of hypoglycemia, requiring the clinician to purposely inquire about the occurrence of previous falls. It cannot be overstated how important this matter is, especially since it may lead to a life-changing injury [56]. Those at high risk for hypoglycemia should be screened for falls as a routine CGA to be added to the CDE. Then, a comprehensive fall risk assessment may follow if falls occur more than once per year, or if there are issues with gait and balance [57].

Urinary Incontinence

Urinary incontinence is frequent in older people with diabetes. It can worsen quality of life, depression, disability, morbidity, and mortality [58, 59]. Similar to other geriatric syndromes, it is rarely due to a single disease. Older patients with diabetes are exposed to diabetes-related factors, such as uncontrolled diabetes with hyperglycemia, leading to glycosuria, polyuria, and from there, urinary incontinence, which can then become a hazard if the patient has other detrimental ongoing issues, such as impaired mobility, or falls risk. In addition, the pharmacology of Sodium Glucose Co-Transporter 2 inhibitors would increase the risk for urinary incontinence, and also increase the risk for urinary infections, which are also associated with urinary incontinence.

A study of community-dwelling older adults with diabetes identified geriatric factors (e.g., inability to ambulate or transfer independently) as important predictors for urinary incontinence in the setting of diabetes and frailty [60].

The intervention is to inquire about symptoms, incorporate those into the clinical decision making, and refer the patient to the corresponding specialists. Nevertheless, we recommend ensuring that reversible factors are considered, such as glycemic control.

Psychological Domain

Depression, delirium, and dementia are the classic most common geriatric syndromes. Notably, personality disorders and addictions are increasing in prevalence in this age group. In addition, we incorporate the sphere of poor quality of life within this domain.

Dementia

Both obesity and diabetes are recognized as risk factors for cognitive decline [61]. While there is no clear pathophysio-

logic pathway (most likely, it is multifactorial), the epidemiological links between diabetes and dementia are quite strong. The current understanding of cognitive decline and dementia put them closer with diabetes and cardiometabolic dysfunction. Alzheimer's disease is the sixth leading cause of death in the United States and is the fifth leading cause among people aged 65 years and over [62]. Compared to those without diabetes, older adults with diabetes are 50–100% more likely to develop dementia, and the risk is greater with longer diabetes duration, poorer glycemic control, and coexistent chronic vascular complications [63]. Furthermore, as another example of the interconnection between geriatric domains, patients with dementia are at greater risk for falls [64].

Thus, the evaluation of cognitive function in older adults with diabetes is warranted, especially for the oldest and those with longer duration of disease [65]. We would suggest additional interest for those patients who volunteer symptoms of memory dysfunction, or who volunteer having issues managing their pharmacologic interventions for diabetes. Quite often, clinicians are used to developing very accurate and complex insulin regimens, but must realize that as plan of care that is not feasible to be effectively implement, will not be efficacious, and only look good on paper. Hence, understanding the cognitive function of the older patient with diabetes will facilitate strategizing targets and interventions. Notably, an earlier detection and diagnosis of dementia will provide additional benefits and opportunities, such as to address proper resources and support, and increase the understanding by providers and family to start dealing with the dementia disease.

Depression

The incidence of depression in diabetes is double than in the general population [66], and it becomes a greater problem in the older population. This is not only due to diabetes-related issues, such as the impact from diabetic complications [67], but also because of age-related issues, such as advancing age, personal loss of function, loss of friends and family support. Furthermore, depression as a separate disease in and of itself will often require pharmacologic therapy, which will further increase the complexity of the case, and negatively impacts diabetes outcomes, such as glycemic control [68], self-care [69], and greater risk for diabetes complications, creating a vicious cycle. Moreover, a study evaluating a survival analysis between younger and older adults with diabetes (and controlling for covariables) found that depression increased mortality risk in the group aged 65 and older (78% greater than in those without depression), while there was no major difference in the younger group [70].

Poor Quality of Life

Older adults have an increased prevalence of multimorbidity and lower QOL [71]. They also present greater coexistence of diabetes and depression [72], which as discussed, negatively impacts HRQOL, diabetes itself, and its outcomes [73].

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial compared intensive versus standard glycemic control. They used SF-36 to evaluate HRQOL and found intensive glycemic control did not lead to QOL benefits (no change) [74].

Social Domain

Elder abuse, social isolation, poverty, lack of family or social support are common scenarios affecting the older person. The social network of people decreases, as family and friends may age and die, or become ill and dependent themselves, so that they are no longer part of the support system. In the general population with diabetes, the economic costs from diabetes are composed of direct (management-related costs) and indirect (work absenteeism, reduced productivity at work and at home, reduced labor force participation from chronic disability, and premature mortality) [75]. In the geriatric older person with diabetes, it is possible that the latter may be less frequent (since many have already retired). However, the costs of management may actually be higher than in younger patients, if we consider the natural history of the disease, which may require a greater number of medications to achieve control, as well as the development of complications and the increase in life expectancy [76–78]. The economic situation can be a major constraint for those who are depending on insurance status and family support, an important resource that could be lacking more in this age group.

Food Insecurity

While it appears that this scenario is gaining more prevalence, it is possible that what has increased is the detection and awareness for this social issue. Food insecurity increases the older patients' vulnerability and risk to develop hypoglycemia. A study reported that patients with limited income have 40% greater risk of having food insecurity and inadequate glucose control [79]. Another study evaluated food insecurity in patients with homelessness, and of those who screened positive and had diabetes, 43.5% reported hypoglycemia symptoms [80].

Table 66.2 Addressing geriatric syndromes in the assessment of older patients with diabetes

Domain	Syndrome	Assessment and intervention
Medical	Polypharmacy	Medication reconciliation at each visit. For each prescription, ask yourself the question: does the patient benefit from this medication (dose, frequency) at this moment?
	Multimorbidity	Older patients are at greater risk for new diseases or complications. A patient could have been in the healthy category by the last visit, but now present after a stroke. Then, his targets and approaches need to be adjusted accordingly
	Malnutrition	Involve the nutritionist team
Functional	Impaired mobility	Consider if the patient has the functional ability to carry the proposed plan of care
	Falls	Ask if the patient has fallen in the past year
		Observe gait and balance while the patient walks into the office
		If these issues are present, the patient has falls risk, refer to the local geriatrician, or falls clinic
		In addition, adjust the glycemic regimen. Avoid hypoglycemia. Avoid regimens with increased risk for hypoglycemia
	Urinary incontinence	Ask if the patient has any issues with urinary incontinence
		Offer referrals to the geriatrician, urologist, gynecologist
		Avoid hyperglycemia
		Consider caution with medications that increase glycosuria
	Frailty	If the patient reports involuntary weight loss, fatigue, weakness, muscle loss, decrease the intensity of the glycemic regimen, avoid hypoglycemia, and refer the patient to a geriatrician
	Self-care deficit	If the patient has ≥2 limitations for IADLs, suggested HbA1c target is between 7.5 and 8%
		If the patient has ≥2 limitations for ADLs, suggested HbA1c target is between 8 and 8.5%
		Ensure the primary care or geriatrician is involved, to facilitate support at home or living situation
		Adjust pharmacologic regimens accordingly. Especially, if the patient has issues with medication management, consider regimens compatible with home health nurse services
	Dementia	Counsel the patient on the potential role for diabetes, but once the dementia disease is established, the priorities shift toward patient safety, avoidance of hypoglycemia
		Refer the patient to the neurologist or geriatrician for further assessment
	Depression	Refer the patient to the geriatric psychiatrist team, aiming to improve depression, as its relationship with glycemic control is bidirectional
	Food insecurity	Adjust glycemic targets, avoiding agents with the highest risk for hypoglycemia. Counsel on strategies to decrease antihyperglycemic medications if eating less and/or losing weight. Refer the patient to the primary care team and social worker team, to address potential community resources

Special Consideration for Diabetes Management in Older Adults

This book offers separate chapters addressing lifestyle, nutrition and exercise, obesity, and pharmacologic interventions. We would emphasize the consideration for modest intentional weight loss as a desirable outcome, as long as it is compatible with the broad comprehensive plan of care for the management of an older patient with diabetes [33]. Exercise interventions in this age group are effective and feasible to implement, providing multiple health benefits beyond diabetes control [81].

Most notably, there are no large randomized clinical trials aiming to prove or disprove the expert-based recommendations (as summarized in this chapter) for the individualized care (targets and strategies) for older adults with diabetes, at different levels of disease burden and health status [82].

Prevention of hypoglycemia is a major priority that should be addressed as soon as detected, through an adjustment of the therapy required to accomplish the established target. Nevertheless, treatment intensification should not be neglected, as macrovascular and microvascular complications should still be prevented in this age group.

Regarding geriatric syndromes, we do not suggest that all practices taking care of diabetes perform a complete geriatrics assessment. First of all, we recommend awareness to this geriatric issues, and then provide a few practical suggestions to address these issues (Table 66.2).

Hypoglycemia in Older Adults: Primary and Secondary Prevention

Hypoglycemia is associated with cognitive impairment, both acute (erratic and irrational behavior, confusion, impaired vision and balance, which can result in falls or accidents) and chronic (leading to dementia) [83]. A prospective cohort study that followed 16,667 patients with diabetes without dementia at study entry found that severe hypoglycemia was associated with greater risk of dementia [84]. However, in

frail, elderly patients with diabetes, avoidance of hypoglycemia, hypotension, and drug interactions due to polypharmacy is of even greater concern [85].

Hypoglycemia events require a clear understanding of their etiology to avoid a recurrence. Details on the history may reveal that the patient accidentally injected the correct dose twice because of forgetting an earlier dose, or that the patient was interrupted during a meal that remained unfinished. In both scenarios, the regimen may remain effective and safe if the events are isolated and conditions do not change. However, recurrent events can be a sign of cognitive decline or early self-care deficits. Regardless of this, glycemic targets need to be adjusted, and further coordination of services (formal or informal) will be required in order to deliver the injectable therapeutic plan and to avoid hypoglycemia.

Secondary Prevention

While one isolated event of hypoglycemia due to a very specific and likely isolated scenario (e.g., patient describes that skipped a meal due to an urgent phone call, which ultimately led to a hypoglycemic event), it is feasible to continue the same regimen, and emphasize education to prevent any future events.

However, if there is evidence for recurrent events, the team needs to address:

- Patient-related factors.
- Modifications to the pharmacologic regimen.
- Reassess glycemic targets.

Primary Prevention

We recommend especial care for those patients at the highest risk (older, on insulin or sulfonylurea, low HbA1c). Considering the potential devastating consequence from even one adverse event (e.g., hypoglycemia leading to a fall, hip fracture, institutionalization, death), we recommend providers to consider strategies to identify patients in whom hypoglycemia has not been present, but who remain at high risk. Our Miami VA team collaborates with the leaders in diabetes care for the Veterans Administration in the USA, fostering the use of electronic tools to detect patients at high risk and avoid overtreatment [86]. While this specific approach might only apply to our healthcare system, the concept could be translated to other healthcare systems.

Pharmacotherapy

Finally, Table 66.3 presents a summary of considerations regarding specific pharmacologic agents and strategies for the management of diabetes in the older patient.

Table 66.3 Special considerations for pharmacologic therapy of diabetes in older adults [7, 14–16, 87]

Order of priority	Pharmacologic agents	Advantages	Disadvantages
Standard first line	Metformin	– No hypoglycemia	– GI side effects are easily countered by always taking with meals
		– Safe and effective	– Risk of vitamin B12 deficiency: monitor and supplement
		– Lowers CV and cancer risk	– The risk for lactic acidosis is actually very low
1	Dipeptidyl-4 inhibitors (Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin)	– Low hypoglycemia risk	– CV and heart failure risk (saxagliptin)
		– Weight neutral	– Increased upper respiratory infections
		– Safe and effective (especially when aiming for less than strong reductions in HbA1c)	– Expensive
			– Limited long-term data in older adults
1	Sulfonylureas (Glimeperide, Glipizide)	– Effective	– Moderate risk hypoglycemia (glyburide is contraindicated)
		– Long-term experience in this age group	– Weight gain
		– Lower CV risk	– Patients losing weight or doing exercise require close monitoring (increased risk for hypoglycemia)

Table 66.3 (continued)

Order of priority	Pharmacologic agents	Advantages	Disadvantages
1	Sodium Glucose co-transporter 2 inhibitors (Canagliflozin, Empagliflozin, Dapagliflozin, Ertugliflozin)	– Low hypoglycemia risk	– High cost
		– Lower weight	– GU infections and urinary incontinence, especial care is required in this age group
		– Lower systolic blood pressure	– Risk for volume depletion, orthostatic hypotension, possibly falls
		– Improve CV risk/mortality (empagliflozin, canagliflozin), renal (empagliflozin)	– Limited long-term data in older adults
1	Glucagon-like peptide 1 receptor agonists (Exenatide, Liraglutide, Albiglutide, Dulaglutide, Lixisenatide, Semaglutide)	– Low hypoglycemia risk	– High cost
		– Lower weight	– GI side effects
		– Reduce CV risk (liraglutide)	– Risk for acute pancreatitis (exenatide and liraglutide)
		– Convenient formulation (daily or weekly)	– Risk for acute kidney injury (exenatide)
2	Long-acting insulin (Glargine, Detemir, Degludec)	– Effective	– Hypoglycemia risk
		– Long-term experience in this age group	– Weight gain
2	GLP-1RA and insulin fixed combinations (insulin glargine + lixisenatide, insulin degludec + liraglutide)	– Effective	– Moderate hypoglycemia risk
		– Convenient formulation (daily or qod)	– High cost
			– Not applicable to all subjects (e.g., not for those who require high dosages)
3	Alpha-glucosidase inhibitors (Acarbose, Miglitol)	– Mild to moderate hypoglycemia risk	– Frequent dosing schedule
		– Effective (especially when aiming for less than strong reductions in HbA1c)	– GI side effects might not be countered easily
			– Contraindication with chronic renal failure (miglitol)
3	Thiazolidinediones (Pioglitazone)	– Low hypoglycemia risk	– Suspected CV risk, heart failure exacerbation
		– Convenient formulation (daily)	– Suspected risk for bladder cancer
4	Intermediate-acting insulin (NPH)	– Long-term experience in this age group	– High risk for hypoglycemia
			– Weight gain
			– Schedule requires at least two injections per day to cover basal needs
4	Pre-mixed insulin	– Long-term experience in this age group	– High risk for hypoglycemia
	70/30 (NPH + regular, NPH + aspart)		– Risk for BID regimens would leave lunch time uncovered
	75/25 (lispro protamine + lispro)		

Multiple-Choice Questions

1. Geriatric syndromes in diabetes management:
   (a) Are of exclusive competency of geriatricians
   (b) **Are determinant and essential in the assessment and plan**
   (c) Are only secondary to glycemic control
   (d) Are uncommon and irrelevant for the clinical outcomes
2. Geriatric syndromes include all of the following except:
   (a) Polypharmacy
   (b) **Type 2 diabetes**
   (c) Persistent pain
   (d) Urinary incontinence
   (e) Falls
3. Macrovascular and microvascular diabetes complications are associated with:
   (a) Cognitive function
   (b) Nutritional risk
   (c) Self-care deficit
   (d) **All of the above**
   (e) None of the above
4. Polypharmacy:
   (a) Is an expected consequence of aging
   (b) **Represents a geriatric syndrome by itself**
   (c) Supports the use of multiple anti-diabetic medications in this age group

(d) Is essential to address patients' needs
(e) Increases costs and non-adherence

5. Each medical visit is an opportunity to address the following aspect of drug treatment:
   (a) Patients' compliance with medical orders
   (b) **Striving to reduce medications when there is no certainty that benefits outweigh the risks**
   (c) The opportunity to add new medications
   (d) The adequate use of **over the** counter medications
   (e) Encourage the use of high-cost medications that these patients can afford
6. Patients who will benefit less from intensive regimens:
   (a) Are extremely rare
   (b) Are less years of education
   (c) Are the ones with less comorbidities
   (d) **Are the ones with six or more comorbidities**
   (e) Are the ones with cardiovascular disease
7. Diabetes in older patients is a risk factor of:
   (a) **Malnutrition**
   (b) Falls
   (c) Dehydration
   (d) Peripheral artery disease
   (e) All of the above
8. The functional domain in the elderly includes all of the following except:
   (a) **Intelligence**
   (b) Eating
   (c) Vision loss
   (d) Hearing loss
   (e) Cooking
9. The following factors account for the increased risk of falls in elderly with diabetes:
   (a) Impaired gait
   (b) Loss of vision
   (c) Cognitive impairment
   (d) Polypharmacy
   (e) **All of the above**
10. Intensive glycemic control in the elderly clearly and remarkably improves quality of life in the elderly with diabetes:
   (a) True
   (b) **False**

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Further Reading

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Part XI

Novel Therapeutic Approaches: Evidence-Based and Others

The Artificial Pancreas

67

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Abbreviations

AP	Artificial pancreas
CGMS	Continuous glucose monitoring system
FDA	US Food and Drug Administration
HbA1c	Hemoglobin A11c
iOS	Apple operating system
MPC	Model predictive control. A controller algorithm
PID	Proportional integral derivative. A controller algorithm

Objectives

- Describe the need for an artificial pancreas.
- Describe the history of artificial pancreas.
- Describe the components of an artificial pancreas.
- Describe the algorithms used in an artificial pancreas.
- Describe the clinical testing of an artificial pancreas.
- Describe the current and future devices.

Introduction

The artificial pancreas is an imprecise term that can mean a bioengineered product, such as an islet cell transplant, gene therapy to replace the pancreas, or the combination of a continuous glucose sensor, an insulin pump (with or without a glucagon pump), and a computer with an algorithm to control the delivery of insulin. In this chapter, we will consider only the last. This is an exciting topic with products being developed by an unusual consortium of academics, the JDRF, the NIH, the FDA, the Helmsley Foundation, and medical device companies. The first artificial pancreas was approved by the FDA in October of 2016 and was first marketed in June 2017 [1].

History

The first attempt at an artificial pancreas was a hybrid external device that measured venous glucose and delivered IV insulin. It was created by Kadish and colleagues in 1964 [2] and was followed over the next 10 years by a series of 5 hybrid devices, one of which, the Biostator, was commercially available [3, 4]. The Biostator worked with a complex, expensive dual lumen catheter, measuring venous glucose and delivering IV insulin. It drew some blood into its tubing, mixed with reagents and measured the glucose. It used the glucose value with an algorithm to deliver insulin and control the blood glucose. It did this very well. The Biostator was a tremendous research tool and had some medical therapy applications, but was too big, too complicated, too invasive, too expensive, and used too much blood to be used long term by individual patients (Fig. 67.1).

The pathway of development soon split, with some working on an implantable device, whereas others worked on a totally external device (Fig. 67.2). Implantable devices got an early start with the development of implantable insulin pumps by Infusaid, Siemens, and Minimed (1980–1981). In 1986 a fully automated artificial pancreas with an IV glucose monitor was tested by Minimed. Because of multiple problems including frequent catheter blockage, sensor fouling, and the invasiveness of the system, further work on the project was suspended.

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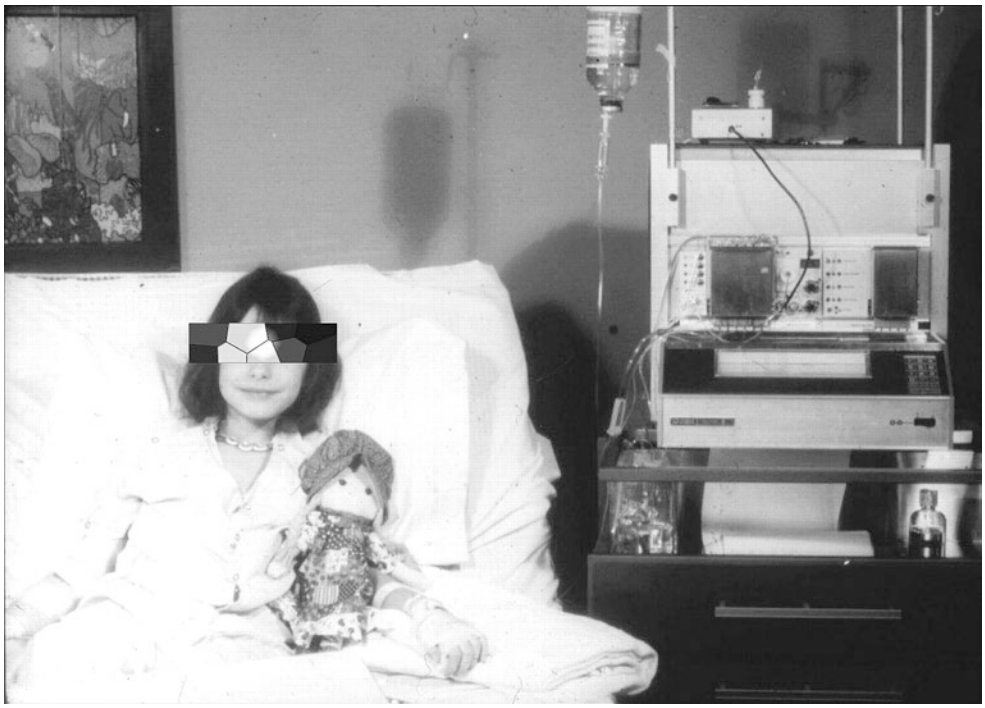

Fig. 67.1 The Biostator, the first commercially available artificial pancreas. (Courtesy of William Clarke, University of Virginia)

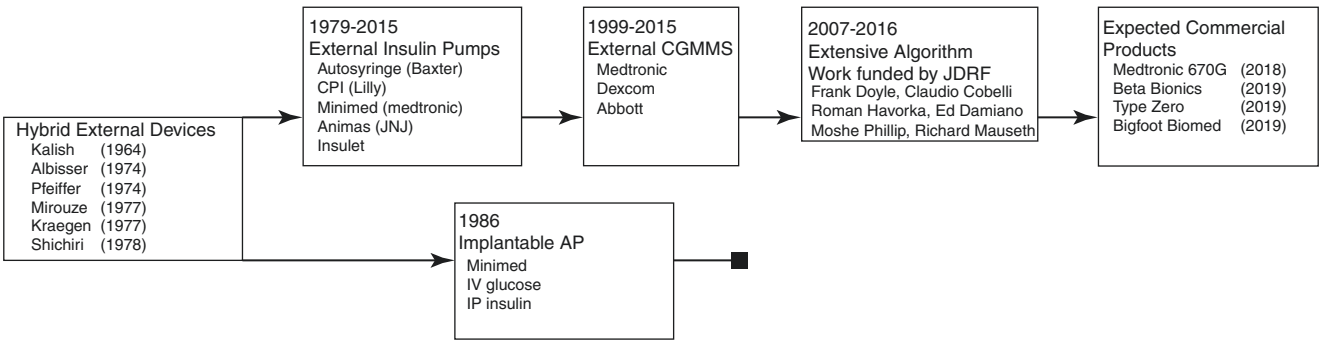

Fig. 67.2 Timeline of development of the Artificial Pancreas

Work on an external artificial pancreas progressed slowly, as the individual components, the insulin pump, and the subcutaneous continuous glucose monitor progressed. A major stimulus to the development was the decision by the Juvenile Diabetes Research Foundation in 2007 to extensively fund research on artificial pancreas algorithms. The project led by Aaron Kowalski set up 8 major artificial pancreas centers and funded research on three different types of algorithms: Proportional Integral Derivative (PID), Model Predictive Controller (MPC), and Fuzzy Logic systems. With their funding for the basic science and clinical studies and their coordination with the major stakeholders, the field progressed rapidly and the first artificial pancreas was approved in September 2016. Special thanks for helping this development should also go to the NIH which had multiple special award cycles for the artificial pancreas and to the FDA which set up a special committee to coordinate regulation of the artificial pancreas.

The Medtronic 670G, first marketed in June, 2017, is the first artificial pancreas, but many new systems are on their way with additions of a modular approach (Type Zero), addition of glucagon (Beta Bionics), and a leasing approach (Bigfoot). Second generation systems using better insulins, smaller devices, and extending the wear time are also in development.

Technology

Components of an Artificial Pancreas

Insulin Pump

An artificial pancreas consists of at least three components, an insulin pump, a continuous glucose monitoring system, and a computer, running an AP algorithm (Fig. 67.3). To understand the artificial pancreas, you need to fully under-

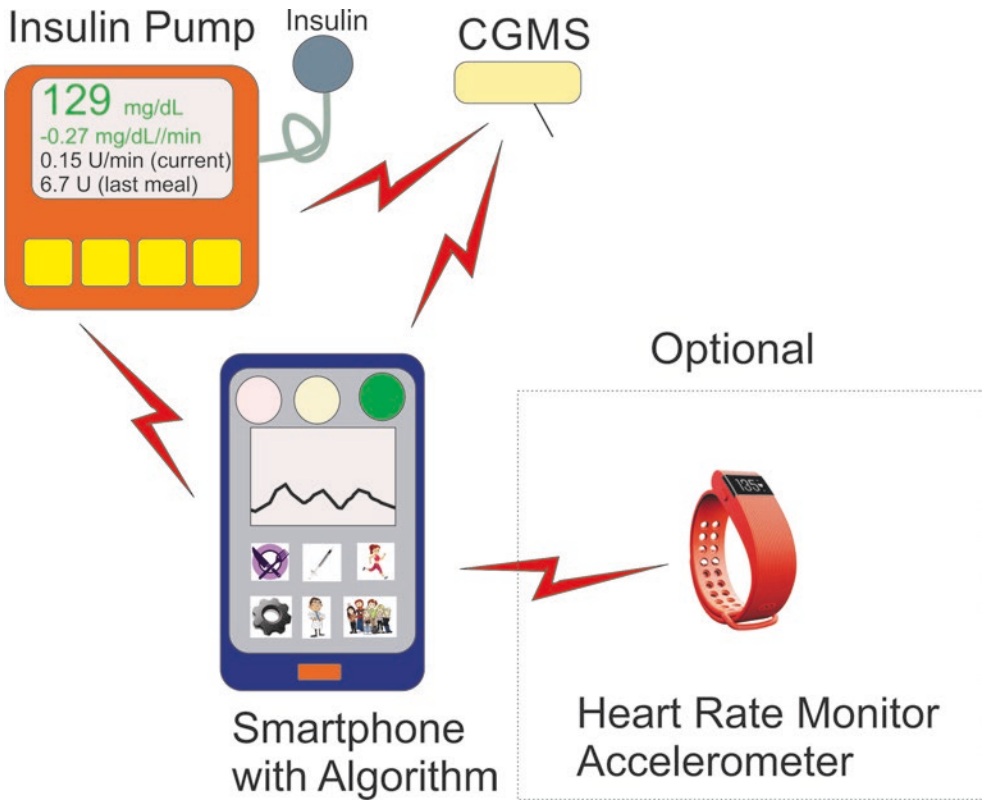

Fig. 67.3 Components of an Artificial Pancreas System

stand an insulin pump, continuous glucose monitoring (CGMS), and intensive insulin therapy. You should review those chapters before proceeding here.

Modern insulin pumps are fully digital. The digital motors are capable of infusion rates as low as 0.05 U/min and as high as 10 U/min with about 5% inaccuracy. They need to communicate with the controller and for an artificial pancreas they also need to communicate with the Computer/Smartphone and generally do so with Bluetooth 4.0 or later. In practice, they also often communicate with the CGMS system. The pumps can work without the artificial pancreas algorithm and should the AP fail, the patient can use the pump as an open loop system.

Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) has been available in some form for almost 20 years but have only become very accurate in 2015. These systems monitor glucose frequently (every 1 to 5 min) rather than continuously and they do not measure blood glucose but rather the glucose in the interstitial space which lags blood glucose by 5–15 min. The best current systems work well in an artificial pancreas. They report glucose every 5 min, have median errors of about 10 percent, and can connect to a controller with Bluetooth 4 or later. Appropriate systems are available as a needle catheter lasting 1–2 weeks and an implantable system that lasts 6–12 months.

Most interesting is the development of a CGMS system built around the needle of an insulin pump catheter, expected to be released sometime in 2017.

Computer

Early experimental systems used laptop computers. As computers got smaller, some systems used netbook computers. Most algorithms for an artificial pancreas do not require extensive computing power and can easily be run by the best of current smartphones. There are experimental systems that run on the Apple iOS and others that run on the Google Android operating system. Additional advantages of running on a smartphone include availability of broadband internet connections and the ability to transmit directly over cellular networks (like texting). There are now smartphones with dual SIMs, so that the personal telephone system and the operating system of the AP are separate. The Medtronic 670G has a computer built into the insulin pump.

Algorithms

For an artificial pancreas, there are 3 common types of algorithms [5]. They differ in their basic approach to calculating the amount of insulin needed at any point.

PID

The first controllers for modern artificial pancreas systems are the PID or proportional, integral, derivative controllers.

These controllers, well established in industrial processes, assess the error in the system, *i.e.,* the difference between the current glucose and the desired glucose using three terms, as seen in Fig. 67.4.

The first term is *Proportional*, a function of the difference between the current glucose (in red) and the desired glucose (in green), shown in the figure as a black two headed arrow. The greater the discrepancy from the desired glucose, the more insulin the controller will suggest.

The second term is *Integral*, a function of the length of time the glucose has been different than the desired glucose. This term is a function of the area under (or above the curve if hypoglycemic) the curve, *i.e.,* the integral of the difference over the past time (shown in yellow). The higher this term, the more insulin the controller will suggest.

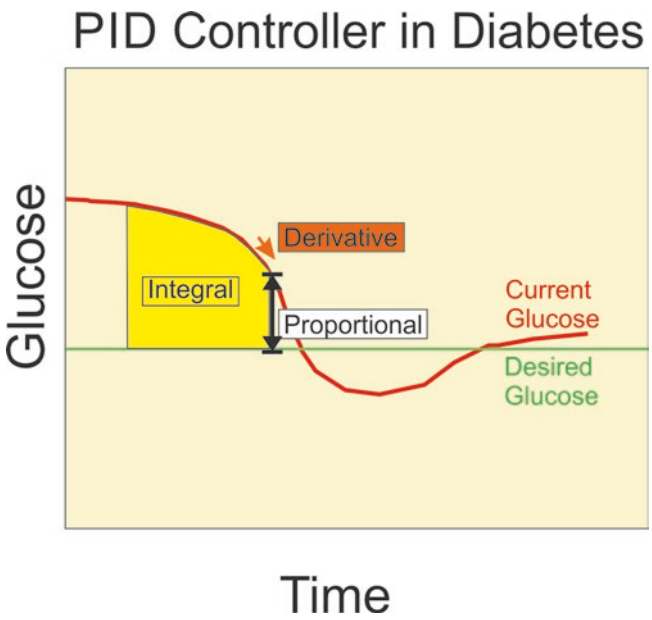

Fig. 67.4 PID control of glucose

The last term is *Derivative*, a function of the slope of the glucose curve (shown in orange). The more rapidly the current glucose is approaching the desired glucose, the less insulin the controller will suggest (if approaching from above).

Thus, the PID controller evaluates the current glucose (proportional), the past glucose (integral), and the future glucose (derivative).

PID controllers are very stable and have been incorporated into the first implanted artificial pancreas and the currently only FDA approved artificial pancreas, the Medtronic 670G.

Model Predictive Controller

Model Predictive Controllers are also very stable "industrial" controllers. Figure 67.5 shows a block diagram of a simple MPC, adapted from Lunze et al. [6]. In this controller, the glucose is separately evaluated to optimize the model parameter and to compare to the current glucose target. These feed the controller, which is based upon the model of diabetes with various food, glucose, and insulin compartments (glucagon too in some) and parameters for the movement among them. The MPC controller generates an insulin infusion rate, which is tested for safety then applied to the patient, altering the glucose value and the process repeats. Variations on this basic approach use glucagon, are modular, or learn from previous days.

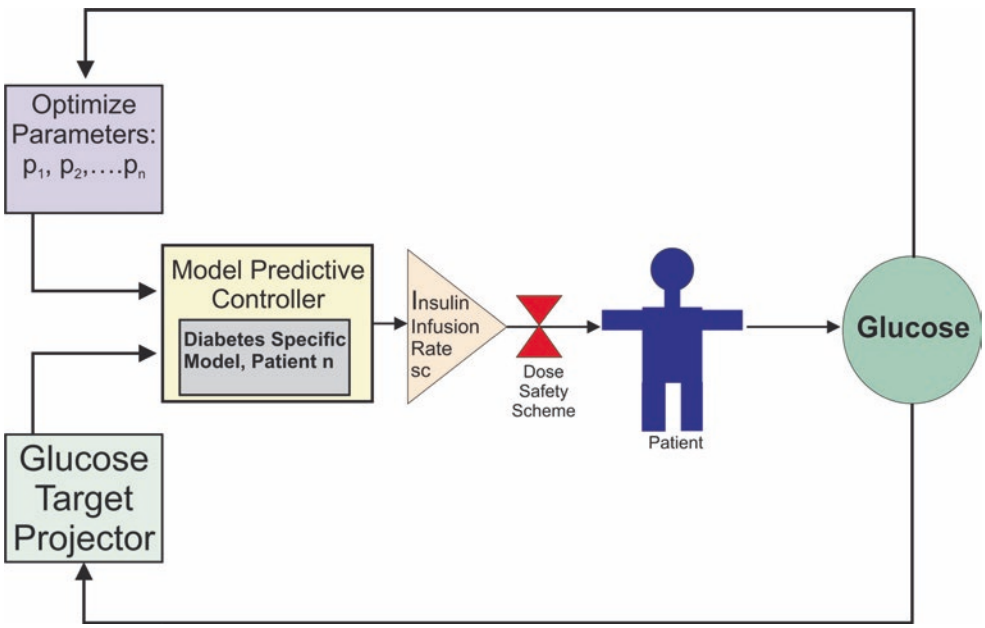

Fig. 67.5 Block diagram of a simple MPC

Fuzzy Logic

Fuzzy logic controllers use analog processes and fuzzy logic principles to mimic the approach a skilled diabetes caregiver would use to manage glucose levels. The MD Logic Artificial Pancreas was the first approved algorithm for an artificial pancreas, being cleared by the European Union in 2015, but there was no hardware approved with it, so there was no product. Another major fuzzy logic system is currently under development by Dose Safety.

Clinical Testing

Evaluating an Artificial Pancreas

Clinical Trial Structure

Clinical trials of the artificial pancreas go through 2 stages after individual components are validated. The first part is feasibility, usually done in 3 parts. The first trials are always done in a clinical research facility with medical personnel always readily available. The second set of trials are often done at a hotel or a diabetes summer camp with medical personnel nearby. The subjects can participate in activities of daily living although a nurse will generally accompany them the first time. The last part is usually a short home trial of 2–4 weeks. The subjects are often remotely monitored and medical personnel are available by phone at all times. Most of these trials will have 15–30 subjects. The second part is the pivotal trial, usually done at home. Twenty-five to 100 subjects are followed at home for 3–6 months.

Safety

Mild hypoglycemia is common in type 1 diabetes with about 20,000 to 40,000 episodes occurring daily in the USA [7]. Serious hypoglycemia occurs about once every two years. Thus, the most important safety feature of an artificial pancreas is no increase in hypoglycemia (a reduction in hypoglycemia would be considered an effectiveness outcome). Similarly, ketoacidosis occurs in about 2–4% of patients with type 1 diabetes each year and we would expect this and episodes of hyperglycemia to be no higher with an artificial pancreas [8, 9].

Effectiveness

Tests of effectiveness are tricky. The gold standard for effectiveness is hemoglobin A1c (HbA1c). This marker, however, is improved by hypoglycemia. Thus, a new therapy could eliminate hypoglycemia and result in an increased HbA1c. Thus, the time in the normal range as determined by CGMS is also important. Most clinical trials have reported normal values as Time in Range (TIR) of 70–140 mg/dL or 70–180, low values as time <70, and high values at time >180 as well as the number and severity of hypoglycemia and the number of hyperglycemic events.

Clinical Trials of Artificial Pancreas Devices

The clinical trials of the devices being currently tested are remarkably similar. All eliminate most of the hypoglycemic episodes in the tested patients. Hemoglobin A1c has generally fallen slightly but glucose time in range 70–180 mg/dL has increased, generally to the 70–80% range. This achievement is dramatic, since the trials are generally done in patients who are already in very good glucose control.

Available Devices

As of August 1, 2017, only a single device has been cleared by the FDA and marketed to patients with Type 1 diabetes, the Medtronic 670G. The AP uses a Medtronic insulin pump and CGMS and a PID algorithm that is built into the pump.

The major clinical trial had 124 participants who used the device for 3 months. The trial demonstrated a difference in the average glucose values and a decrease in HbA1c from 7.4 to 6.9. There was a dramatic decrease in hypoglycemia and time in hypoglycemia and an increase in time in range 70–140 and a corresponding decrease in time > 140. Overall it was an impressive demonstration of the power of the artificial pancreas, even compared to patients already using an insulin pump and a CGMS.

Future Devices

Other groups are close to reaching the market. Type Zero diabetes has taken a modular approach. They have built each part of the controller into a separate module. Thus, they test each module for safety and effectiveness and add new modules to the system as they are approved. The system is designed to be run on an Android phone but is otherwise hardware independent. Much like devices that work with your computer, every device that works with the Type Zero device will have a "driver" to allow the device to communicate with the algorithm. Some devices may also need a module to ensure proper use of the device.

Beta Bionics, a company commercializing the algorithms of Boston University, is developing a system using two pumps, delivering insulin and glucagon. Because there is currently no stable liquid glucagon formulation, their first device will be an insulin-only device.

The third company is Bigfoot Biomedical. They are using a proprietary algorithm developed by the company. Their commercial model, unique in many ways, is to lease the device and all disposables for a single monthly fee. This simplifies the usage of the device and the reimbursement.

Cyber-Security

A few years ago, it became clear the insulin pumps could be "hacked" and forced to deliver a lethal dose of insulin. The risk is much higher with an artificial pancreas. The Diabetes Technology Society set standards for diabetes medical devices to prevent such attacks. Using the Common Criteria, they suggested at least a level 4 security was needed. This level of security needs to be designed with the device and built into it. It cannot be added on later. Thus far, none of the companies creating an artificial pancreas had used these standards.

Concluding Remarks

- The artificial pancreas is now available after 20 years of promises.
- Current devices are hybrid devices. The patient still needs to enter information about diet and exercise.
- More systems are on their way with better algorithms and a larger choice of devices.

Questions

1. What are the components of an Artificial Pancreas?
2. What types of algorithms are available? How do they work?
3. Describe currently available devices.
4. How are AP systems clinically tested?
5. What are the advantages of an AP?

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Unproven Therapies for Diabetes

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Introduction

Prevalence and History of Diabetes

There has been a pronounced upsurge in worldwide diabetes prevalence during the past few decades, more notably in developing countries, owing to the rapid globalisation and changing lifestyles. Diabetes-associated complications such as coronary artery and peripheral vascular disease, stroke, diabetic neuropathy, amputations, renal failure, and blindness also add to this burden. According to the recent IDF estimates, one in 10 are living with diabetes. Diabetes-related deaths (6.7 million) were also higher than the total number of deaths caused by HIV (0.068.0 million), tuberculosis (1.5 million), and malaria (0.0627 million) combined. Nearly 537 million people worldwide are estimated to have diabetes, and IDF has raised the concern that by 2030 almost 643 million people and by 2045 almost 783 million adults will have diabetes [1, 2].

The history of diabetes dates back to 3500 years ago, where the first-ever mentioning of clinical features similar to diabetes mellitus is found to have been made in the greatest Egyptian medical document 'Ebers Papyrus' in 1500 BC (Ebbell 1937). Descriptions of this devastating disease have also been found in ancient Indian and Chinese medical literature, as well as in the work of ancient Greek and Arab physicians [3]. Indian physicians named the condition 'madhumeha' or 'honey urine' observing that the urine from diabetes affected individuals attracted ants and flies [4]. Apollonius of Memphis is believed to have coined the term 'diabetes' in 230 BC, meaning 'to pass through' and it was Aretaeus of Cappadocia (second century AD) who provided the first accurate description of diabetes [5]. Later on the Indian physician Sushruta and the surgeon Charaka (400–500 AD) differentiated between the two types of diabetes primarily based on their occurrence in lean or overweight individuals [5, 6].

Remarkable advancements in understanding and management of diabetes took place in the nineteenth century, mostly attributable to the significant progress achieved in various scientific disciplines. Until the discovery of insulin in the 1920s by Banting and colleagues, diabetes treatments mostly adapted highly crude methods for which the success rates were extremely poor [5] and physicians of those times used to make interesting recommendations such as 'oil of roses, dates, raw quinces and gruel, jelly of viper's flesh, broken red coral, sweet almonds and fresh flowers of blind nettles' which represented a variety of beliefs and practices of the times [7]. There are also mentions of opium being prescribed liberally [7, 8] (probably for easing the symptoms of complications like gangrene). Of note, in 1897, the average life expectancy for a 10-year-old child diagnosed with diabetes was 1.3 years, compared with 4.1 years for a 30-year-old person [9].

The first-ever scientific remedy, discovered in 1922, and awarded the Nobel Prize in 1923, insulin turned out to be a major advancement in treating diabetes and enabled patients to live near-normal life [3, 10]. The first-ever oral scientific remedy Sulphonylurea was added to the treatment armamentarium, only in the 1950s. Consequently, other oral scientific remedies with diverse mechanisms of action such as metformin, glucosidase inhibitors, and insulin sensitizers were discovered, enabling better management of the disease. Currently, our treatment armamentarium consists of a vast array of technologies and therapeutic options to make individualised treatment more of a reality. Depending on the type of diabetes and its aetiology, patients may be treated with oral drugs or injectables or sometimes a combination of both. For absolutely insulin-deficient type 1 diabetes mellitus (T1DM) patients, insulin pump therapy or multiple daily insulin injections are the only scientifically recognised modalities of therapy; in the absence of them, subjects are likely to die. With such advances in modern medicine, a dra-

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matic improvement in life expectancy has been noted after 1940. As per WHO, the average lifespan of a child born in 2015 is predicted to be 71.4 years whereas earlier estimates of global life expectancy were 30.9 years in 1900, 46.7 in 1940, 61.13 in 1980 [11, 12].

Complementary and Alternative Medicine

Definition and Epidemiology

According to National Center for Complementary and Integrative Health (NCCIH), a subsidiary of the National Institutes of Health (NIH), USA, Complementary and Alternative Medicine (CAM) are those healthcare approaches that have developed outside the realm of conventional medicine. Types of complementary and alternative health approaches fall into one of the 2 subgroups, viz. natural products or mind and body practices. Natural products (available widely and often sold as dietary supplements) consist of herbs (or botanicals), vitamins and minerals, and probiotics. Mind and body practices include a variety of procedures or techniques administered or taught by a trained practitioner or teacher (e.g. yoga, chiropractic and osteopathic manipulation, meditation, massage therapy, acupuncture, relaxation techniques, tai chi, etc.). However, some approaches may not neatly fit into either of these groups—e.g. the practices of traditional healers, Ayurvedic medicine, traditional Chinese medicine, homoeopathy, and naturopathy [13].

Of the various demographic descriptors and characteristics of users documented for an inclination towards CAM, more consistent ones include being female, more highly educated, wealthier, employed, and having private health insurance [14–17]. Research has also demonstrated that individuals who possess positive health behaviours and exhibit fewer health risk factors are more frequent CAM users [18].

According to the statistics from 2012 National Health Interview Survey (NHIS), 33.2% of US adults and 11.6% of US children aged 4 to 17 used complementary health approaches. The most commonly used approach was natural products (dietary supplements other than vitamins and minerals). The mind and body approaches most commonly used by adults included yoga, chiropractic or osteopathic manipulation, meditation, and massage therapy. The popularity of such practices might definitely increase in coming years as evident from the data on the percentage of adults who practice yoga. The percentage of followers of this system of practice was found to be increased substantially, from 5.1% in 2002 to 6.1% in 2007 and 9.5% in 2012. As per the survey, nearly 59 million Americans spend money out-of-pocket on complementary health approaches, and their annual spending totalled around 30 billion dollars [19, 20].

Possible Reasons Towards CAM Popularity

A vast majority of patients opt for CAM therapies as a complement to conventional care rather than as an alternative choice [21]. In a US-based study, total visits to complementary medical practitioners (629 million) exceeded total visits to US primary care physicians (386 million) [22]. Traditional CAM practices are extremely popular in South-Asian countries, where modern conventional medicines are often inaccessible and unaffordable to the majority of individuals. Therefore despite the perception about the efficacy of modern medicines, traditional medicine continues to relish acceptance among these populations [23].

Several factors have been noted as reasons for the extensive use of these rather scientifically unproven methods of CAM therapies (Table 68.1). Dissatisfaction arising from conventional therapies, at times, clubbed with higher treatment expenses, concern over side effects of drugs, an urge to have a grip on the course of the disease, and a notion of CAM therapies being compatible with patient's values and beliefs [17, 24–27] are some of them. Patients' expectations of their efficacy [27, 28], advanced stage of the disease [29, 30], experiences with conventional healthcare professionals and complementary medicine practitioners, and 'healthcare pluralism' are also identified as the reasons for this widespread acceptability of CAM therapies. The later term describes the fact that when people become ill they can opt for seeking assistance and treatment advice from diverse sources ranging from friends/family, conventional/CAM practitioners etc. which essentially will have an impact on their treatment choices [31, 32]. Analysis of the 2002 National Health Interview Survey pointed out that around six million American adults had opted CAM therapies predominantly because they found conventional medical treatments unaffordable. Among 63% of the individuals who faced such cost constraints, herbal remedies were found to be the most popular approach [33].

Table 68.1 Reasons for CAM popularity

- Belief that CAM practices are devoid of any side effects and are totally safe
- Non-invasive nature
- Easy accessibility
- Advanced stage of the disease and unpleasant experiences with conventional healthcare professionals
- As recommended by someone close (family members, friends, etc.)
- Pleasant therapeutic experience
- Modern conventional medicines being inaccessible and unaffordable
- Dissatisfaction arising from conventional therapies
- Poor doctor–patient relationship
- Insufficient time with doctor
- Concern over side effects of drugs
- An urge to have a grip on the course of disease
- Notion of CAM therapies being compatible with patient's values and beliefs

CAM Therapies for Diabetes Management

Many Anti-diabetic Medications Have a Natural Origin

Many of the standard conventional drugs have a history of natural origin. However, administering them in their natural form may not be of much benefit. Phytochemicals or compounds present in the natural sources often serve as 'lead' molecules for the synthesis of bioactive compounds and also newer analogues could be derived from some of them. This search for novel bioactive from nature plants, animals, or microflora still continues to widen our treatment armamentarium. Estimates suggest that around one-half of all licensed drugs that were registered worldwide in the 25 year period prior to 2007 were either natural products or their synthetic derivatives [34, 35].

Over 400 traditional plant treatments for diabetes have been reported and only a few of them have undergone valid scientific scrutiny to prove their safety and efficacy [36]. Metformin, a popular anti-diabetic drug and widely accepted first-line agent, was derived from a traditional anti-diabetic plant *Galega officinalis* (Goat's Rue or French Lilac) [37] whose active ingredient was found to be glargine or isoamylene guanidine. While guanidine and certain derivatives were found to have toxic effects, the biguanides (two linked guanidine rings) turned out beneficial and were available for therapeutic use since the 1950s [38]. Further research confirmed antihyperglycaemic efficacy of metformin without causing overt hypoglycaemia or weight gain. Metformin in addition to its antihyperglycaemic properties also stands out for its effects beyond glycaemic control such as improvements in endothelial dysfunction, haemostasis and oxidative stress, insulin resistance, lipid profiles, and fat redistribution [39, 40]. The United Kingdom Prospective Diabetes Study demonstrated that early use of metformin reduced cardiovascular mortality and increased survival in overweight and obese T2DM patients beyond that expected for the prevailing level of glycaemic control [41]. This proven efficacy, safety, beneficial cardiovascular and metabolic effects, and its capacity to be associated with other anti-diabetic agents make metformin the first line of choice for T2DM patients [42] and is included in the World Health Organization (WHO) list of essential medicines [43]. Phlorizin, isolated from the bark of apple trees, was found to cause glycosuria [44] but later led to the discovery of better analogues with SGLT2 inhibiting activity such as dapagliflozin, empagliflozin, and canagliflozin [45, 46].

The discovery of insulin by Frederick Banting and Charles Best in 1921 was indeed a major breakthrough in the treatment of diabetes and it all began with a murky concoction of canine pancreas extract [34, 47]. Likewise, Exenatide and highly accepted insulin with anti-diabetic activities have their origin from animals. Exenatide, a glucagon-like peptide-1 (GLP-1) agonist, is a synthetic version of exendin-4, a hormone found in the venom of Gila monster *Heloderma suspectum* which was isolated by Dr. John Eng in 1992 [48, 49]. This drug has been approved for use in T2DM management [50].

Apart from anti-diabetic compounds of plant and animal origin, some have been derived from microbes. Examples include Acarbose (from Actinoplanes sp.), Miglitol (from Bacillus and Streptomyces sp.), Voglibose (from Streptomyces hydroscopicus subsp. Limoneus) [46], etc. The alpha-glucosidase inhibitor Acarbose used in T2DM is a pseudo-oligosaccharide isolated from the culture broths of various actinomycetes [51]. It is probably the most widely used digestive enzyme inhibitor for the treatment of T2DM, acting on α-glucosidase, α-amylase, sucrase, and maltase, but without insulinotropic properties [52]. With regulated research and controlled clinical trials, there is a higher probability that many more natural agents could be incorporated into the modern stream of medicine.

Prevalence and Patterns of CAM Use Among Diabetes Patients

According to Villa-Caballero and colleagues, the presence of diabetes is a predictor of CAM use and ethnicity determines the types of CAM followed. Of the different CAM modalities, biologically based practices (e.g. dietary supplements, herbal products, and botanical products) are the most commonly used and studied for treating diabetes [53, 54] which is probably due to their wider and cheaper availability, and also being inherent in the cultures and ancestral beliefs of the individuals. Egede et al. using the data from the 1996 Medical Expenditure Panel Survey compared the prevalence and pattern of use of complementary and alternative medicine (CAM) in individuals with and without diabetes and identified factors associated with CAM use. Analysis revealed that diabetes affected individuals were 1.6 times more likely to use CAM than those without diabetes and the most commonly used CAM therapies among diabetes patients were found to be, in the order of importance, nutritional advice and lifestyle diets, spiritual healing, herbal remedies, massage therapy, and meditation training [55]. Another study from Israel reported that almost every fourth patient with diabetes uses CAM [56]. India, a country with a rich history of traditions, rituals, and healing practices, has a very high CAM use of 67% among its diabetic population, of which majority (97%) used Naturopathy, which often included herbalism [57]. An ethnographic study conducted in Kerala revealed that the patient's perceptions of disease as well as its management are influenced by their cultural background

and environmental resources. Many of them frequently used Ayurvedic and traditional herbal medicines as supplements to conventional therapy [58].

The National Center for Complementary and Alternative Medicine (NCCAM now re-named as NCCIH) conducted an analysis of the data from National Center for Health Statistics, Centers for Disease Control and Prevention (CDC), and demonstrated that, among adults with T2DM, 30.9% used complementary medicine for any reason, but only 3.4% used complementary medicine to treat or manage their T2DM versus 7.1% of those with T1DM. Almost 77% of the T2DM patients, who used complementary medicine to treat/manage their disease, used it in conjunction with their conventional prescription medicine. Furthermore, individuals with more severe diabetes were predicted to be more likely to use complementary medicine. The most prevalent types of complementary medicine therapies followed included diet-based interventions and non-vitamin/non-mineral dietary supplements [30]. In a study that determined the nature and prevalence of dietary supplement use among chronically ill children, 60% of the patients with T1DM reported using supplements to manage their disease and 31% admitted non-prescribed use [59].

Concerns with CAM Therapies

The widespread use of CAM practices poses several risk factors (see Table 68.2) such as the patients getting overloaded with consecutive unsuccessful therapeutic measures owing to false diagnosis, running into life-threatening situations, adverse effects, and hidden costs of treatment. Opting for these unconventional practices might delay the initiation of effective modern conventional treatments and thereby increase the chances of treatment failures and unbearable treatment expenses [60–64]. Drug–herb interactions, compromised quality of the products due to adulteration or presence of inappropriate amounts of active ingredients, lack of proper regulations on various CAM practices and CAM practitioners, underdeveloped research, poor quality of clinical trials, false claims and fake publicity, absence of proper communication with health practitioners, etc., are all known to be the contributing risk factors towards the failure of CAM therapies [65–68].

Table 68.2 General concerns associated with CAM therapies

- Adverse drug interactions
- Patient's belief of receiving optimum therapy and finally running into life-threatening conditions and increased treatment costs
- CAM products not meeting quality standards due to reasons such as:
  - Products being adulterated with modern medicines to achieve/enhance the efficacy
  - Inadvertent incorporation of unintended constituents due to errors with herb selection, good manufacturing procedures, etc.
    - Intra- and inter-product variations
    - Mislabelling of the contents
- Poor quality of the clinical trials making it difficult to arrive at a definite conclusion regarding efficacy and safety of CAM practices
- Patient's prejudice that CAM therapies are natural and safe, which increases their tendency towards self-treatment practices and use of over-the-counter products
- Lack of proper communication between the patients and health practitioners regarding CAM use
- Polypharmacy with CAM and conventional treatments resulting in decreased medication adherence and more negative quality of life
- Lack of stringent regulations to guard against quackery in CAM practices

Compromised Quality of CAM Products

Lack of proper adherence to manufacturing, marketing, and storage protocols might lead to deterioration in product quality, viz. contamination with undesirable substances; intra-product and inter-product variations; mislabelling of the contents, misidentification, etc., which leaves us highly unsure regarding their safety and efficacy [61, 69–71]. Considering the example of herbs, they do not have a consistent, standardised composition and different plant parts have a different profile of constituents. Furthermore, several factors such as climate, growing conditions, time of harvesting, and post-harvesting factors such as storage conditions and processing are all known to influence the content and concentration of constituents. Although standardisation of many of these products has been implemented, it may not be always feasible since active constituents of many botanicals are still unknown [31]. In a meta-analysis conducted, high variability in ginsenosides levels in ginseng across different source parameters, viz. ginseng-type, assay technique, and ginsenoside type, was shown to result in high variability in their efficacy. This is a warning signal that the reported safety and efficacy data of a particular product may highly differ when compared to other over-the-counter batches, preparations, varieties, and species of the herb [72].

Many US-manufactured and Indian-manufactured Ayurvedic medicines that were sold over the Internet were adulterated with unacceptable levels of lead, mercury, or arsenic [73], and serious consequences were also reported with the use of 'herbal' products that contained 'hidden' active drug compounds or heavy metal contaminants [74–78]. The Centers for Disease Control and Prevention (CDC), USA, had reported lead intoxication from Ayurvedic medications among pregnant women [79]. Since 2007, the FDA has imposed an import alert on certain Ayurvedic products to prevent such products from entering the United States [80]. Accidental or intentional contamination of CAM products with conventional drugs (e.g. corticosteroids) or poisonous substances (e.g. heavy metals, pesticide residues) and microorganisms is also reported [81, 82]. Chinese 'herbal' creams were found to contain corticosteroids [83], and some Indian

Ayurvedic remedies contained heavy metals [74]. Likewise, deterioration in the quality of 'homoeopathic' remedies [84, 85] as well as that of therapeutic essential oils [86], is also a major concern. Another classic example is 'Chinese herb nephropathy' where weight reduction pills supposed to contain the herb *Sephania tetrandra* were inadvertently contaminated with nephrotoxic herb *Aristolochia fangchi,* causing nephropathy and/or cancer in women attending a slimming clinic in Belgium [87–89].

Complications from Drug Interactions

When CAM products such as herbal medicines or dietary supplements are used concomitantly with conventional drugs, a very common practice, there may be a potential for drug–product interactions. Product–product interactions may also occur when many of these products are used concurrently [90]. These interactions often alter the pharmacokinetics or pharmacodynamics of conventional drugs, thereby altering their absorption, distribution, metabolism, and/or excretion [66, 67]. Herbs possessing hypoglycaemic activity like ginseng, garlic, and bitter melon are all reported to have additive effects in patients taking oral hypoglycaemics or insulin [72, 91–93]. In contrast, dietary gums (e.g. gum guar) usually prescribed to overcome postprandial hyperglycaemia were found to reduce the absorption of hypoglycaemic agents like metformin and glibenclamide by prolonging gastric retention [92, 94, 95]. Since diabetes patients are often burdened with many other comorbidities, the majority of them would require lifelong polypharmacotherapy (multiple medications) and hence stand at increased risk of such harmful drug interactions [96].

Underdeveloped Research and Poor Quality of Clinical Trials

Unlike conventional medicine, CAM in general lacks an established research infrastructure and therefore many of the already available scientific evidence are methodologically weak or outright flawed [97–101]. Measures such as the implementation of CONSORT guidelines [102, 103] for reporting and the establishment of a 'field' for CAM in the Cochrane database [104] have allowed us to make a more reliable assessment of the safety and efficacy of these systems of medicinal practices [101].

False Claims and Fake Publicity

Alternative medicine is widely promoted among the public and some of them even claim these therapies to be highly effective with no side effects [105]. The inherent notion among the public that these therapies are 'natural' and hence 'completely safe' enables easier exploitation by advertisers and commerce. The absence of stringent regulations in many countries can allow exaggerated claims to be made and this is more pronounced in areas of commerce that are difficult to control, for example products sold over the internet [106]. It is often seen that the lay literature and even certain 'professional' texts based on some CAM practices make unsubstantiated medical claims as well as encourage self-treatment for even some serious conditions [31, 107].

In India, 'The Drugs and Magic Remedies (Objectionable Advertisements) Act', 1954, controls the advertising of drugs and restricts advertisements of such 'wonder-drugs or remedies' [108].

Lack of Proper Regulations and Policies

Among WHO's 194 countries 97 countries have a national policy on TM/CAM and only 124 countries regulate herbal medicines [109]. The WHO has published a series of technical guidelines and reviewed regulations on herbal medicines in the document 'Regulatory Situation of Herbal Medicines: a Worldwide Review' [110]. In the United States, national non-governmental organisations, such as the Accreditation Commission for Acupuncture and Oriental Medicine, the American Board of Medical Acupuncture, the Council of Chiropractic Education, etc., accredit education in some of them, while most other nations are devoid of these [68]. In the United States prior to 1994, CAM supplements were classified as either foods or drugs depending on the intended use and later Dietary Supplement Health and Education Act (DSHEA 1994) framed a better definition for 'dietary supplement'. It effectively took out any product containing a vitamin, mineral, herb, or amino acid marketed as a supplement to the normal diet from obtaining USFDA approval. This legislation allows such products to forego the stringent approval processes and does not require any proof of their safety and efficacy before being marketed. However, this has led to the situation where many of them are available over the counter even in grocery stores [61, 111].

Similar is the situation of CAM practitioners in many countries where they are not regulated in any manner. There are no systems in place to evaluate the training or expertise of these practitioners [68, 112–114]. In rural areas where timely access to treatment is challenging, this poses a major problem. Many of the times, local practitioners become the primary point of approach and thus the lack of authentic therapists can aggravate the situation [68, 114]. Therefore, imposing restrictions on CAM practitioners without any acceptable educational qualifications and adopting standards of practice should be given due priority to minimise such practice risks [115].

Absence of Proper Communication with Health Practitioners

When the extent of patients' utilisation of complementary medicine, and their knowledge and attitude regarding the same, was studied by Giveon et al., more than half of the respondents believed that natural drugs are safe with no side effects. Users may not relate their symptoms to CAM and not disclose its use to their physician, leading to complications such as delayed diagnosis and treatment, delaying or replacing a more effective form of treatment or even compromise the efficacy of certain conventional drugs. The situation becomes even worse when CAM users are advised by the healers to discontinue the use of prescription drugs, particularly in those with chronic disease conditions [116]. CAM practitioners usually do not encourage inquiries regarding the constituents of their preparations, and most patients are least interested to know about the same as they consider such preparations to be 'natural', otherwise 'safe'. Healthcare professionals are mostly unaware of CAM use by their patients and are not consulted prior to their use [117]. Unfortunately, there are also instances where even when the physicians are aware of their patients using such unproven remedies, they may not be trained to recognise potentially serious side effects [33]. Therefore, it becomes practically impossible to apprehend whether CAM therapy played any significant contributory role towards the efficacy or failure of conventional treatment [118].

In its Position Statement on 'Unproven Therapies', ADA raises the concern that most patients do not disclose the use of alternative medicine and hence conventional practitioners need to specifically ask their patients about the same. ADA continuously evaluates the usefulness of different CAM therapies, their potential risks to the patients and so on to characterise the effectiveness of such treatment modalities. They, however, do not recommend the use of any such unless their safety and efficacy has been established by current standards [119]. In the United Kingdom, the House of Lords' Select Committee on Science and Technology's report on CAM recommended statutory regulation of CAM practitioners and recommended regulatory bodies of healthcare professionals to develop guidelines on CAM competence and training. By this regulation, conventional healthcare professionals are expected to have a basic knowledge of such therapies, and conventional health providers may have interactions with state registered CAM practitioners [120].

Concerns with Other CAM Therapies

Homoeopathy, for example, even though accepted widely, the methodological quality of the trials based on this system of therapy is found to be very poor. Arguments are still on in the view whether homoeopathy is superior to the placebo as a treatment concept [121–123]. Adverse effects can occur if the remedies are not highly diluted since most but not all homoeopathic remedies are devoid of active molecules. Many of the homoeopathic prescriptions include remedies containing arsenic or other highly poisonous substances and in case such a remedy is used in its undiluted form by any chance, it could result in life-threatening consequences [124]. Therapies involving mechanical techniques might cause detrimental effects. Chiropractors, for example, apply a controlled force to a spinal joint and can cause vertebral arterial dissection after upper spinal manipulation [125]. Acupuncture (stimulates specific points on the body by inserting thin needles through the skin) can cause complications like pneumothorax [126, 127], cardiac tamponade [128–130], and central nervous system injuries [131]. Serious infectious complications (like hepatitis, HIV, sub-acute bacterial endocarditis, etc.) can also arise when the practitioners are not concordant with aseptic techniques [132, 133].

Impact of CAM on Diabetes Treatment Outcomes

In a survey conducted among participants of SEARCH for Diabetes in Youth, patients who followed a 'CAM diet' reported a better quality of life (QOL), whereas supplement use and stress reduction activities resulted in decreased QOL. Moreover, children who did not follow any CAM practices experienced lesser treatment barriers [134]. In another study among patients with T2DM and/or cardiovascular disease, higher CAM use was highly correlated with a decreased quality of life in. This was attributed to the negative effects of using multiple therapies where some of them could, in fact, interfere with conventional care [135]. CAM use was also found to decrease the adherence towards prescribed medications in different patient populations [136] including those with diabetes. Patients with T2DM who used CAM were almost 6.16 times less adherent to their prescribed diabetes medication than the non-CAM using counterpart [137, 138]. One of the major reasons postulated towards this diminished adherence is that CAM users are both logistically and psychologically burdened and may need to sacrifice part or all of their prescribed diabetes medication so as to continue using CAM. Another reason pointed out was that the patients believed in CAM healers more than the conventional practitioners [136].

In spite of branding 'natural' and a long history of use, most of these traditional medicines are not necessarily safe. As noted earlier, use of CAMs may delay the use of effective modern conventional treatments and cause adverse effects. Health risks can arise from issues such as drug–herb interactions, adulteration of the products, or the presence of inappropriate amounts of active ingredients in the products [65–67]. Diabetic patients frequently undergo treatment for associated diseases such as hypertension, neuropathy, car-

diovascular disease, and so on. While evaluating the effect of CAMs, it is important to understand drugs and drug interactions in depth, and the failure to record the present history of CAM use may lead to problems with other medicines that the patient uses [65, 139]. Instances such as renal failure with use of the dietary supplement chromium picolinate, hepatotoxicity with ingestion of sheep bile, and poor outcomes in a group of patients after abrupt stopping of insulin injections to initiate various CAM therapies have been documented [140]. Another very common drawback noted with CAM products used in diabetes is that when combined with insulin or secretagogues, the patient may experience additive hypoglycaemia due to drug interactions [53]. Herbal medications that claimed to treat diabetes were found to illegitimately incorporate modern medicines with chlorpropamide [141], glibenclamide [142] etc. with a view to enhancing their efficacy and finally resulting in undesirable outcomes. Lead poisoning from herbal remedies is another grave concern [143, 144]. Furthermore, CAM practitioners, as well as manufacturers of such ethnic herbal remedies, even provide patients with fatal advice such as urging them to stop all medicines of diabetes and injections while following CAM therapies which makes the situation even worse [142, 145]. Nutritional advice and lifestyle modifications form essential components of diabetes management, and such recommendations are also often prescribed by many of the CAM providers. The risk lies with the fact that such advice often differs from those endorsed by conventional diabetes care providers and even does not adhere to the guidelines of ADA for diabetes management. Whether these additional nutritional advice and lifestyle diets complement and reinforce ADA guidelines or conflict with the conventional system is another matter of debate [55]. American Diabetes Association's Standards of Medical Care do not support the use of vitamin, mineral, or herbal supplements for diabetes management, due to the lack of sufficient evidence [146].

Fatty liver, non-alcoholic steatohepatitis (NASH), and subsequent cirrhosis are becoming very common in diabetes and associated disorders. Despite the lack of studies or evidence, more and more people are accepting natural remedies with the belief that they are effective with no side effects. But here, the dictum, 'medications with efficacy will also have side effects' stands true. However, those who are advising as well as using it are totally unaware of adverse events. Several observational studies have reiterated the potential hepatotoxic effects of herbal preparations, including asymptomatic minor transaminase elevations, acute and chronic hepatitis, granulomatous hepatitis, asymptomatic to severe cholestasis, sinusoidal obstruction syndrome, acute liver failure requiring transplantation as well as progression to cirrhosis and portal hypertension [194].

Several systematic reviews have been published that weighed the impact and efficacy of various CAM therapies on preventing and treating diabetes. Recently, the effect of Ayurveda on treating diabetes mellitus was studied by Sridharan et al., and the effect of Chinese herbal medicines on impaired glucose tolerance or impaired fasting blood glucose was assessed by Grant et al. Both these reviews pointed out the benefits of following these traditional systems of medicine in treating diabetes or pre-diabetic conditions. The authors, however, stop short of recommending such practices citing the biased nature of certain studies and lack of sufficient evidence [99, 147]. An overview of beneficial and adverse effects identified with some of the widely used herbs, herbal products, and supplements for diabetes management is provided in Table 68.3.

Table 68.3 Commonly used herbs and supplements for diabetes management [53, 64, 69, 95, 148–151, 194, 195]

Name of herb, herbal product, or supplement	Beneficial effects/ hypothesised mechanism of action	Side effects/drug interactions and contradictions
Cinnamomum zeylanicum	Increases insulin sensitivity by increasing PPAR (alpha and gamma) expression, increases cellular glucose entry by enhanced insulin receptor phosphorylation and translocation of GLUT4 glucose transporter to the plasma membrane, promotes glycogen synthesis	Skin irritations if used topically, interacts with secretagogues and causes hypoglycaemia, coumarins possess anticoagulant, carcinogenic, and hepatotoxic properties
Gymnema sylvestre	Insulin secretagogue, increases glucose uptake promoting enzymes, stimulates and increases beta cell number	May cause hypoglycaemia when combined with secretagogues
Bitter melon (*Momordica charantia*)	Hypoglycaemic action, insulin mimetic, enhances glucose uptake by tissues, inhibition of glucose producing enzymes, enhances glucose oxidation (G6PDH pathway)	Gastrointestinal discomfort, hypoglycaemic coma, favism, haemolytic anaemia in persons with G-6PDH deficiency, abortifacient activity of α and β momorcharin, hypoglycaemia when used with sulfonylureas
Fenugreek (*Trigonella foenum-graecum*)	Insulin secretagogue, hypoglycaemic activity, lipid-lowering effects, increases HDL cholesterol, slows carbohydrate absorption and delays gastric emptying, inhibits glucose transport, increases insulin receptors, improves utilisation of peripheral glucose	Diarrhoea, gas, uterine contractions, allergic reactions, drug interaction with hypoglycaemic agents, anticoagulant drugs, MAO inhibitors, contraindicated in pregnancy

(continued)

Table 68.3 (continued)

Name of herb, herbal product, or supplement	Beneficial effects/ hypothesised mechanism of action	Side effects/drug interactions and contradictions
Guar gum	Alters gastrointestinal transit and delays glucose absorption, lipid-lowering effects by decreasing its absorption and increasing bile excretion	Gastrointestinal upset, may delay the absorption of drugs, possibility of hypoglycaemia when combined with secretagogues, additive lipid lowering when used along with antihyperlipidemic agents
Noni *(Morinda citrifolia)*	Reduces fasting glucose, HbA1c, serum triglycerides, and LDL cholesterol and improves insulin sensitivity (data limited to in vivo and in vitro studies)	Severe acute liver failure; acute hepatitis with portal inflammation and periportal necrosis
Gurmar *(Gymnema sylvestre)*	Gymnemic acid type A, phytochemical compound present in shoot tips and seeds, is one of the most potent hypoglycaemic components. Some of the alkaloids and saponins in the plant also act as appetite suppressants	Hepatotoxicity, may cause acute hepatitis
Chromium	Lipid-lowering effects, insulin sensitising effect by decreasing tyrosine phosphatase activity or direct effect on insulin receptor by increasing tyrosine kinase activity at the insulin receptor, may promote glucose transport	Renal toxicity and dermatological reactions, potential hypoglycaemia with secretagogues, steroids may decrease chromium levels, vitamin C may increase chromium absorption
Alpha-lipoic acid	Improves insulin resistance and increases glucose effectiveness	Can affect thyroid function in patients with thyroid disease, might produce allergic skin reactions, abdominal pain, nausea, vomiting, diarrhoea, and vertigo
Omega-3 fatty acid/fish oil	Lowers triglycerides, anti-inflammatory, anti-platelet, hypotensive, slight increase in blood glucose	High intake might cause bleeding, fish meat to be eaten with caution due to contamination with high levels of methyl mercury; may increase LDL, drug interactions with anticoagulant and anti-hypertension drugs

Evidence regarding the use of other systems of CAM for diabetes is also in its infancy and in fact, the available little evidence cautions the patients and the practitioners regarding their safe and effective use. Studies which assess acupuncture are methodologically problematic mainly due to reasons such as the procedure has no adequate control condition, treatments in daily practice are mostly individualised, short duration of the studies, etc. [152–154]. None of the trials conducted in diabetes patients could provide convincing evidence on acupuncture for treating conditions like insulin resistance [154], diabetic gastroparesis [155], and diabetic peripheral neuropathy [156]. Practitioners and patients who support acupuncture for diabetic neuropathy may also bear in mind the increased risk of acupuncture needle site infection with high blood glucose levels [157]. Opting for acupuncture after discontinuing conventional therapy recently led to the death of a 30-year-old T1DM individual in India [158]. 'Sweet therapy' is another peculiar diabetes treatment practised in Kerala, which claims to stimulate the sleeping pancreas to secrete insulin by intake of glucose-rich foods such as sweet desserts. However, the long-term serious implications of such modalities on the health of the patients are not documented.

Trials that investigated the effects of tai chi [159–163] and qi gong [152, 164] on diabetes also could not reach any definitive conclusions. Such mind–body therapies which involve movements can at best be considered as alternative modes of exercise [165, 166]. The perceived advantage of these therapies is that they can be performed at almost any level of exercise tolerance when compared to traditional exercise, and thus might be helpful for increasing movement and activity especially for some persons with diabetes such as older and obese individuals [152]. They might also be helpful in imparting behavioural and psychological changes and thereby help patients to cope with the disease and increase their quality of life [167]. However, neither yoga [168, 169] nor tai chi [170–172] has been shown to have any significant impact on improving the glycaemic status. In diabetes patients who follow practices such as massage, Therapeutic Touch, Healing Touch, and Reiki, appropriate blood glucose monitoring and titration of anti-diabetes medications should be recommended when blood glucose levels become lower as pain and discomfort decrease. During energy therapy, catecholamines like epinephrine and norepinephrine get released which can increase lipolysis and thermogenesis, leading to increased energy expenditure and weight changes [157].

Recommendations for a Prospective CAM Use

Proper Patient–Physician Fit and Judicious Choice of Therapies

The current hypothesis is that treatment settings influence a patient's mindset and even influence the effects of inter-

ventions. This speaks volumes regarding the importance of maintaining a positive relationship between the patient and the caregiver in achieving commendable treatment efficacy [121]. Unfortunately, most of the times patients following conventional medicine were dissatisfied with the manner of communication by the practitioners, were worried about the side effects of pharmacotherapy, and also felt the lack of a holistic treatment approach. On the other hand, CAM seemed to reinforce a patient's own self-healing capacity. Alternative therapists tend to spend more time with their patients which help to develop a good patient–physician fit, and many of the patients appreciated this approach [173].

CAM use often remains underreported and thus a lack of proper communication between patients and healthcare providers can often end up in treatment failures or adverse events. Care providers should put in their efforts to understand the motivations behind a patient's CAM use and be prepared to counsel such patients, when needed, about the options available and should be able to assess, as well as present information to the patients regarding the expected risks, side effects, benefits, and choices regarding self-management and its cost to the patient, helping them to make an informed choice [53, 136, 174]. In patients who persist on following CAM, it is advisable to identify the effects of each of the components of these medications so that patients can be counselled regarding any contraindications to any of the constituents. Patients should be adequately monitored and warned of the potential side effects, and healthcare practitioners should be aware of the potential interactions between the active components of the alternative medications and other prescribed medications [175]. For individuals exploring supplements, FDA's documents such as 'Tips for the savvy supplement user', 'Tips for Older Dietary Supplement Users', and 'Questions and Answers on Dietary Supplements' might turn helpful (accessible at http://www.fda.gov). A database of natural medicine available at 'www.prescribersletter.therapeuticresearch.com' provides necessary information regarding the usage of herbs and supplements and their safety issues [176]. The American Diabetes Association in two of its articles 'A Step-by-Step Approach to Complementary Therapies' and 'Guidelines for Using Vitamin, Mineral, and Herbal Supplements' has offhandedly acknowledged the popularity of CAM for diabetes and provides a set of approaches that could be undertaken in order to safely integrate complementary therapies into an individual's healthcare plan [177, 178]. In its position statement, ADA proposes to evaluate each questionable diagnostic or therapeutic modalities and recommends proving new and innovative, but unproven, diagnostic and therapeutic measures for patients based on certain preset criteria and also encourages healthcare providers to ask patients about their alternative therapy practices [179].

Proper Regulations and Well-Conducted Research

Although anti-diabetic drugs used in modern medicine have a natural origin [34], administering them in their natural form may not be of much benefit. Randomised clinical trials of herbal medicine interventions too often underreport the crucial characteristics of the intervention, thereby deviating from the standards set by Consolidated Standards of Reporting Trials (CONSORT) [180, 181]. However, with regulated research, there is a higher probability that many more natural agents could be used in modern medicine. Experts recommend that CAM and dietary supplements should be subject to scrutiny similar to conventional medicines by organisations such as the NIH and FDA. Any measure to bypass these may render the healthcare system inefficient, incapable, and dangerous [182, 183]. Adequate or accepted research methodology for evaluating these healthcare practices needs to be developed. Consideration should also be given to increase the overall quality of research, avoid publication bias, protect intellectual property, and also to certify authentic CAM products and practices from illegitimate ones [184].

Integrating CAM into Conventional Care

Although CAM practices lack sufficient evidence, the popularity of such practices is ever increasing and its integration into mainstream health care is much looked at. In certain regions, CAM practices are included under health insurance coverage and certain 'integrated' delivery systems have also been established [15, 185]. While considering the integration of medical systems, apart from emphasising patients' expectations and needs, it should be prioritised that accepted standards of medical and scientific principles of practice remain unaltered [186]. With such integration, patients are believed to get benefited at multiple levels such as better decision-making, enhanced physical and emotional well-being, and gaining knowledge on health-promoting practices (Furnham 1996). Healthcare providers can also get benefitted in terms of greater satisfaction through learning new treatment strategies and developing skills to implement them [187]. Thus a more integrated system is expected to facilitate discussion and collaboration between the two systems of medicine to improve healthcare delivery [188]. A snapshot of the recommendations suggested towards a prospective CAM use is provided in Table 68.4.

Table 68.4 Recommendations for a prospective CAM use

Developing a proper patient–physician fit that can encourage patients to openly communicate regarding CAM use – Healthcare providers should try to understand patient's motivations behind CAM use so as to choose an optimal treatment plan – Healthcare providers can take efforts to assess, as well as present necessary information to the patients regarding different aspects of CAM use and thus help them make a more informed choice
Validating the safety and efficacy of CAM therapies through well-planned clinical trials that meet quality research standards
Impose proper regulations and scrutiny on CAM practices, products, and practitioners to ensure their safety, quality, and efficacy
Integration of CAM and conventional medical systems by giving emphasis to patient's expectations and needs, without altering the accepted standards of medical and scientific principles

CAM Therapy and COVID-19

The Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has met international health systems with a low level of preparedness and emergency response [189]. A wide range of CAM therapies are being practised worldwide including acupuncture, acupressure, cupping, massage, gestalt therapy, reflexology, muscle therapy, etc. for the prevention and cure of COVID-19 [190]. With a rich history of traditional medicines, countries like China and India explored the effectiveness of their traditional medicines to prevent and cure COVID-19.

In India, the ministry of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homoeopathy) to encourage research in various traditional drugs on COVID-19 established guidelines focusing on multi-pronged approach of Ayurvedic medications, which are already in use for a long time for ailments like fever, cough, and respiratory distress [191].

Evidence from several studies has shown that some plant preparations and spices such as pepper, ginger, cumin, and coriander seeds have anti-viral, anti-bacterial, and anti-microbial properties [192, 193]. Given that some of these preparations lack data related to efficacy, adverse events, manufacturing method, and quality control. However, many preparations are also being propagated without having any scientific evidence.

Currently, there is only limited research from human clinical trials in regard to the effectiveness of CAM in prevention, treatment, or symptom relief in COVID-19.

Conclusion

Even with the advancements achieved in modern conventional medicine, a lot many patients still continue to follow traditional CAM practices due to a variety of reasons such as their perceived safety and efficacy, easy availability or matching with their cultural beliefs and practices, and so on. However, the risk–benefit ratio of these CAM practices on the disease outcomes especially the chronic one like diabetes still remains unproven. Conventional healthcare providers in most cases are not aware of their patients following such modes of therapies and also are not in a position to comment on regarding the same. They should put in efforts to maintain a good rapport with the patients so as to enable open communication regarding CAM use so as to help them make a judicious choice of such therapies. Imposing stringent rules and regulations as well as conducting clinical trials that meet quality research standards can no doubt reveal the true potential of at least some of these age-old practices. With that achieved, the successful integration of reliable and safe CAM practices into mainstream health care can be thought of in order to improve the overall treatment experience and outcomes.

Multiple-Choice Questions

1. Complementary and alternative medicines:
   (a) Are essential additional elements of diabetes management
   (b) **Are healthcare approaches developed outside the realm of conventional medicine**
   (c) Are exclusively medicines
   (d) Include surgical interventions
   (e) Are evidence-based
2. Complementary health approaches:
   (a) Are rarely used
   (b) Are largely used by people with low economic resources
   (c) **Are used by 33.2% of adults in the United States**
   (d) Are used mostly by men
   (e) Represent a minimal amount of healthcare costs
3. Reasons for the popularity of complementary alternative medications include all of the following, except:
   (a) Easy accessibility
   (b) Dissatisfaction with conventional medical care
   (c) Belief of safety
   (d) **High costs**
   (e) Poor doctor–patient relationship
4. Many currently approved anti-diabetic medications have a natural origin:
   (a) **True**
   (b) False
5. Examples of anti-diabetic drugs with natural origin:
   (a) Insulin
   (b) Sulfonylureas
   (c) **Metformin**
   (d) **SGLT2 inhibitors**
   (e) **GLP-1 agonists**

6. The percentage of patients with type 2 diabetes using complementary medicine in addition to conventional prescriptions:
   (a) 15%
   (b) 27%
   (c) 48%
   (d) 60%
   (e) **77%**
7. The use of complementary alternative medications has several risks, including:
   (a) Adverse effects
   (b) Hidden costs
   (c) Overload with unsuccessful therapies
   (d) Lack of proper regulations
   (e) **All of the above**
8. The hypothesised mechanism of action of chromium:
   (a) Insulin secretagogue
   (b) **Insulin sensitizing agent**
   (c) Insulin mimetic
   (d) Inhibits glucose transport
   (e) Alters gastrointestinal transit
9. The hypothesised mechanism of action of guar gum:
   (a) Insulin secretagogue
   (b) Insulin sensitizing agent
   (c) Insulin mimetic
   (d) Inhibits glucose transport
   (e) **Alters gastrointestinal transit**
10. Recommendations for the prospective use of complementary alternative medications involve:
    (a) Recognition as essential elements of management
    (b) Learning about their effectiveness
    (c) **Judicious choice of therapies**
    (d) Combination with standard therapies
    (e) Discourage their use by patients

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Insulin Delivery: An Evolution in the Technology

69

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Introduction

All patients with type 1 diabetes (T1DM) require insulin due to absolute deficiency, and most type 2 diabetes (T2DM) patients require insulin at one time or the other due to progressive β-cell failure, to sustain life [1, 2]. In people with diabetes, the most efficient therapeutic option available to reduce hyperglycemia continues to be insulin even though they experience numerous challenges with the use of insulin including interference with daily living, financial constraints, the complexity of regimens, injection discomfort, and public embarrassment for injecting insulin [3, 4]. Therefore, to avoid the complications related to diabetes such barriers have to be handled with advanced and proven technologies for insulin delivery [5].

Beginning with the syringe for injecting insulin, progressing to insulin pumps, insulin pens, and sensor-augmented pumps, the growth of diabetes technologies accelerated with the introduction of hybrid closed-loop systems, integration with consumer electronics, and cloud-based data systems [6, 7]. These devices have favorably improved patients' perceptions about insulin therapy along with improving their quality of life [8]. However, the right choice and application of diabetes technologies are essential for positive outcomes.

The first manufactured insulin pump was introduced as early as in the 1970s, whereas the first manufactured insulin pen was introduced only in 1985 [9].

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Insulin Delivery Devices

Insulin Vial and Syringe

In 1924, 2 years after the discovery of insulin, Becton, Dickinson and Company (BD) made a syringe specifically designed for insulin injection [10] (Fig. 69.1). Initially, syringes were made of metals and/or glass, which were reusable and after each use, required boiling for sterilization. In 1925, Novo Nordisk launched the first insulin syringe, the "Novo Syringe" (Fig. 69.2). To reduce the extent of needle-associated infections, disposable syringes were developed. In 1954, BD mass-produced the first glass disposable syringes called the BD Hypak. In 1955, an all-plastic Monoject syringe (Roehr Products Inc) was introduced onto the market. In the 1960s, BD introduced the 1-mL LuerLok insulin syringe available with either a detachable needle or a permanently attached needle. Disposable plastic syringes from numerous vendors were available on the market by the mid-1960s [11]. These syringes reduced pain and the rate of needle-associated infections [12]. In spite of all these advances, many patients did not feel to inject insulin 3–4 times a day due to needle phobia.

By 1970, BD manufactured the first one-piece insulin syringe with an integral needle [13]. Following, U-100 plastic insulin syringes with units marking down the side of the syringe came into use [11]. In 1988, the BD Safety-Lok insulin syringe with advanced safety features was introduced. In 2012, BD introduced the BD Veo insulin syringe with an Ultra-Fine 6-mm needle, offering less pain and reduced plunger force to ease the flow of large insulin doses [14]. Due to the reduced risk of intramuscular injections, this syringe has been widely preferred [15]. The FDA approved a U-500 specific insulin syringe designed by BD to address the dosing errors while administering doses from a U-500 vial with a U-100 insulin syringe in 2016 [16]. Instead of the long, large bore-sized and reusable needles used in earlier years, nowadays, small bore-sized and short-length needles (8 mm, 6 mm, and 5 mm) are used for insulin injection.

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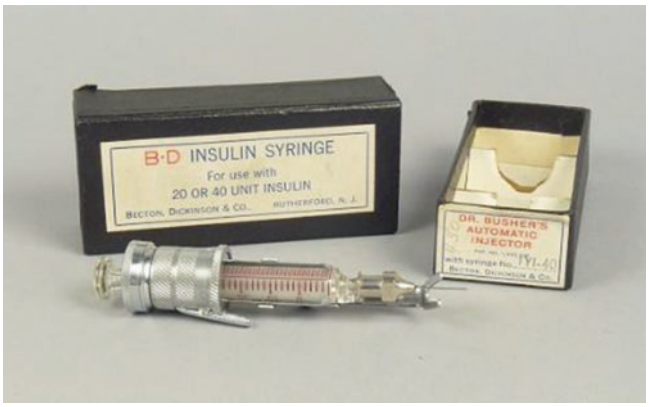


Fig. 69.1 First insulin syringe

Fig. 69.2 Novo syringe

For more than 50 years, vials and syringes have remained as the only option for insulin delivery although "conventional" syringe technology has become less popular in the current era.

Insulin Pen

Due to inconvenience and inaccuracy in preparing the insulin dose, insulin shots using vial and syringe have a lot of challenges [9]. These issues contributed to the development of insulin pens. The introduction of insulin pens was a phenomenal achievement in insulin delivery. In 1985, the first insulin pen, the NovoPen, was launched by Novo Nordisk followed by NovoPen 2 in 1988. NovoPen 2 has a distinct dial-up setting to measure the required dose [17]. In common, pens provide more simple, accurate, and convenient insulin delivery over syringes (Table 69.1). An insulin pen has mainly three components: an insulin cartridge, a disposable short needle, and an incremental "one-click per unit" dosing. These devices can be either reusable or disposable. Reusable insulin pens have a replaceable cartridge whereas disposable pens have a prefilled cartridge and are discarded after use.

Table 69.1 Advantages and disadvantages of insulin delivery methods

Methods	Advantages	Disadvantages
Vial and syringe	• Less expensive compared to insulin pen and pump	• Increased pain at the site of injection versus pen • Inconvenience in carrying • Decreased accuracy when compared to pens • Less patient-friendly
Insulin pen	• Efficient and convenient delivery of insulin • Accurate dosing and flexible because of disposable and reusable options • Ease of injection and time saving • Easy to carry • Better treatment compliance and long-term cost-effectiveness	• More expensive than syringes • Does not allow the mixing of different insulin types • Low dosing
Insulin pumps	• Continuous delivery of insulin • Better glycemic control • Increased patient compliance and acceptance • Decreased hypoglycemia	• More expensive • Increased risk of DKA if pump fails • Injection site infection • Technical and safety issues with the cannula and infusion set (detach, crimp, or leakage) • Can cause skin irritability or hypersensitivity in patients
Intraperitoneal	• Direct insulin delivery to the portal vein • More physiological	• Invasive • More cost • Increased risk of infection and portal vein thrombosis
Inhaled insulin	• Noninvasive • Increased patient compliance • Rapid onset of action (10–15 min) • Better PPBG control	• Reduced bioavailability • Inhalational devices issues • Decreased lung function • Transient cough
Oral insulin	• Increased portal insulin concentration • Noninvasive • Patient-friendly	• Reduced bioavailability
Buccal insulin	• Relatively large surface for absorption • Presystemic metabolism in the GI and liver avoided • The level of vascularization is very high in some areas	• Great variations of permeability among the different areas of the oral mucosa • Reduced bioavailability
Nasal insulin	• No interference with pulmonary functions	• Reduced bioavailability (15–25%) • Local irritation • Nasal irritation
Transdermal insulin	• Needle-free	• Skin irritation, blister, pain and redness • Safety not established

PPBG Postprandial blood glucose

Novo presented the world's first disposable, prefilled insulin pen known as "Novolet" in 1989 [18]. Insulin adsorbs onto the plastic surface of these prefilled pens over time and a precise concentration can be accomplished by legitimate blending. Therefore, the dose accuracy and blood glucose (BG) stability between cartridge changes are increased by pens [19].

The newer insulin pens are more accurate and furnish with safety features such as audible clicks with each dose to improve accuracy and reduce the chances of human errors [9, 20]. Another achievement in the pen device (HumaPen® Memoir™) is integrated with recording the time and date of the last 16 injections [21].

Compared with syringes, pens offer more flexibility, accuracy, discreetness, and long-term cost-effectiveness, providing improved treatment continuity and adherence. Therefore, the use of insulin pens exhibits better glycemic control and has wider acceptance [22, 23]. Despite insulin pens being convenient, less painful, and patient-friendly, they are related with higher cost in comparison with vial and syringe [24, 25].

Technologic refinements over the fundamental features of the earlier versions have produced more advanced insulin pens. Finer and safer needles which are shorter and thinner (31–32 G × 4–5 mm) that offer reduced pain perception and require less thumb force and time to inject insulin have also been developed resulting in improved patient satisfaction [26, 27].

First Generation Insulin Pens

From the 1990s, first-generation insulin pens are available on the market. The prominent insulin pens in this category are multiple generations of durable pens of the NovoPen family, AllStar (Sanofi), and prefilled pens, such as FlexPen, FlexTouch (Novo Nordisk), Humalog Pen, Kwikpen (Eli Lilly), and SoloSTAR (Sanofi) (Fig. 69.3). NovoPen 3, a durable pen allowing a maximum dosage of 70 U, was launched in 1992 (Fig. 69.4). The essential feature of this device was less wastage of insulin while resetting the dose at the dial and push-up buttons. This pen was more economical and was further refined for patient subsegments, such as NovoPen 1.5 and NovoPen Junior. In 1996, NovoPen 1.5 was launched, a shorter version of NovoPen 3, which can hold smaller insulin cartridges. NovoPen3 Demi, the first Novo family member to allow half-unit dose increments, was advertised in 1999. In 2001, FlexPen, a prefilled insulin pen, was introduced. In 2003, NovoPen Junior, with vibrant colors, specifically designed for children with diabetes, was initiated [28]. The NovoPen 4 (dose increments of 1.0 U, maximum dose of 60 U) was launched in 2005. In 2007 and 2008, refilled insulin pens, Kwikpen (Eli Lilly) and SoloSTAR (Sanofi), were launched respectively [29].

Fig. 69.3 First generation insulin pens

Fig. 69.4 NovoPen®

In 2011, Novo Nordisk introduced FlexTouch, a re-engineered version of the original FlexPen. It is the single prefilled insulin pen with an easy touch button, which improves the ease of use and device handling for the patients [30]. In 2012, Sanofi India launched its first indigenously developed reusable insulin pen, AllStar, specifically designed for diabetes patients in India. The key features of this pen are the slim and discreet design, clear dose magnification window, dose arrow on both sides, bayonet cartridge lock, short dial-out distance, penalty-free reverse dialing, audible click sound with every unit dialed and dispensed, and non-rotating dial button during dispensing [31]. In 2017, Junior KwikPen, a prefilled half-unit

insulin pen, was considered to be lighter and smaller than other half-unit insulin pens and was approved on the market.

In 2021, Toustar Reusable Insulin Pen Sanofi was intended to be used in conjunction with the insulin glargine 300 U/mL in a dedicated cartridge (Toujeo® 1.5 mL cartridges) to deliver insulin through subcutaneous injection using commercially available needles. The key features are user can reverse dial without losing insulin and simple "push-to-reset" plunger (no screwing required) [32].

Insulin pen needles of 4 mm, 5 mm, 6 mm, 8 mm, and 12.7 mm lengths are used. The Nano 4-mm pen needle (BD), the shortest pen needle, is more comfortable and easiest to use. These needles require low thumb force and allow higher flow rate and insulin absorption [33].

Next-Generation Insulin Pens

Since 2007, second-generation pen devices or "smart pens" with a memory function were available on the market. These devices have a multidose memory feature that allows storing the date, time, and amount of the previous doses [34, 35]. These devices are unified with USB or Bluetooth features for efficient monitoring and data management. In 2007, Eli Lilly launched HumaPen MEMOIR, the world's first digital insulin pen with memory, and HumaPen LUXURA HD, a reusable pen for people who require insulin dosing in half-unit increments from 0.5 to 30 units. In 2010, Novo Nordisk launched NovoPen Echo, the first insulin pen with memory and half-unit dosing features [36]. In 2012, NovoPen 5, a successor to NovoPen 4 was launched with a simple memory function for use with the 3-mL Penfill cartridge [37].

The newer smart pens are designed to guide the individual with diabetes about the insulin dosage (by means of inbuilt calculators), memory functions to remember the amount and time of insulin dosage, and automatic transmission of insulin dose to the mobile logbook through Bluetooth technologies [12].

Connected Pens

Connected pens are next-generation insulin pens with characteristics that go beyond the memory function. In 2017, Pen System was launched by Companion Medical which consists of a Bluetooth-enabled wireless insulin pen with a smartphone interface and bolus advisor [38]. These pens will automatically record the dose of insulin injected, and the data can be shared with collaborating CGM devices and Glooko's Diasend digital diabetes management platforms and are expected to be synced with Roche's mySugr app [39]. Novo

Fig. 69.5 NovoPen 6 and NovoPen Echo Connected pens

Nordisk's NovoPen 6 and NovoPen Echo Plus also fall into this category of pens (Fig. 69.5). These pens will automatically record the dose of insulin injected and the data will be shared with Dexcom G6 CGM, FreeStyle Libre system (Abbott), and Glooko's Diasend digital diabetes management platforms. Connected pens are furnished with NFC (near-field communication) technology that permits scanning of these devices to transfer the data off to another device [40]. Another advanced innovation in pen technology was Bluetooth/internet-connected insulin pen cap that aids the generation of smart dosing systems through a mobile app for the convenience of T1DM patients who do not use an insulin pump [41].

Even though insulin pens offer the convenience of use, less pain, and better treatment adherence and health outcomes, they have limitations such as difficulty in applying a mixture of insulins, higher cost, and lack of universal insurance coverage [42]. Regardless of the ease of use, pens are mechanically more complex than insulin syringes [43].

InPen Smart Insulin Pen

In 2020, Medtronic launched connected smart insulin pen, the InPen, acquired from Companion Medical. The InPen is the only FDA cleared, smart insulin pen system that combines the freedom of a reusable Bluetooth pen with the intelligence of an intuitive mobile app that helps users administer the right insulin dose, at the right time (Fig. 69.6). The InPen sends dose information to a mobile app and the app uses the glucose levels and a carbohydrate estimate to recommend the dose. It even considers the amount of insulin that is still working in the body, to help avoid low glucose.

Fig. 69.6 InPen with Guardian connect and connected app

Injection Aids: I-Port Advance Injection Port

To reduce the frequency of multiple injections and needle phobia in patients with diabetes, injection aids are also used in practice. In 2016, an injection port was designed known as i-port Advance launched by Medtronic. It is a small and discrete patch, which can be attached to the skin and the device remains adhered to the skin for up to 72 h and allows multiple injections. It is the first device to combine an injection port and an inserter in one complete set which helps to eliminate the need for multiple injections without puncturing the skin for each dose. This device is useful for insulin requiring patients having needle phobia and helps them to accomplish glycemic control effectively [44, 45]. Although there was an initial excitement, this device remains unpopular probably because insulin shots with newer needles are virtually painless.

Insulin Pumps

Insulin pumps are small, computerized devices that imitate the way the human pancreas works by delivering small doses of short acting insulin continuously (basal rate). The device is also used to deliver variable amounts of insulin when a meal is eaten (bolus). Pumps are modernized gadgets for the delivery of insulin and can be used for dispensing insulin in any patient who exhibits the desire to initiate pump therapy and fulfills the criteria for a pump candidate [1].

Continuous Subcutaneous Insulin Infusion (CSII)

In normal physiology, a continuous small amount of insulin secretion from the beta cells of the pancreas reduces hepatic glucose output, and when food is ingested a larger amount of insulin is secreted to maintain euglycemia [46]. The CSII therapy was used by DCCT trial in nearly 40% of the participants in the intensive arm [47]. The current generation of insulin pumps are more patient-friendly due to its smaller size and smart features such as built-in-dose calculators and alarms [46]. The main components of an insulin pump are an insulin reservoir, infusion set, and tubing. The insulin reservoir is connected to the infusion set and a catheter helps to continuously deliver insulin to meet the daily requirement. The pump has user-specific inbuilt programs to dispense insulin at basal rates (slow, continuous) and in incremental (bolus) doses before meals [48]. This characteristic helps in the removal of the inherent variations associated with the injection depth and multiple injection sites that are typical of conventional subcutaneous injections. The infusion site needs to be changed only once every 2–3 days. Therefore, insulin pumps terminating the need for multiple injections on a daily basis can lead to less insulin variation [49, 50].

In 1963, the first portable insulin pump was invented by Dr.Arnold Kadish but it was limited by its size and technical issues [51](Fig. 69.7). In 1979, the first commercial insulin pump was introduced in the USA [20]. In 1976, Dean Kamen introduced the first wearable insulin pump, known as the "blue brick" and later the "autosyringe," and led to the introduction of insulin pump therapy in the same year [52]. The first SOOIL insulin pump was clinically evaluated at Seoul National University Hospital in 1979 [53]. In 1983, MiniMed introduced their first insulin pump, MiniMed 502. In 1986, MiniMed introduced the implantable insulin pump to deliver insulin intraperitoneally. Insulin delivered through this device was absorbed quickly and directly to the portal system [54]. In 2000, new versions of the pump with improved memory and battery life were launched on the market. Later in 2007, implantable insulin pump devices were discontinued by Medtronic.

In the 1990s, new-generation external pumps were released which are comparatively small, compact, handy, and effective. These "smart pumps" have characteristics as built-in bolus calculators, personal computer interfaces, and alarms [55]. The insulin pump models which are approved on the global market are Medtronic MiniMed,

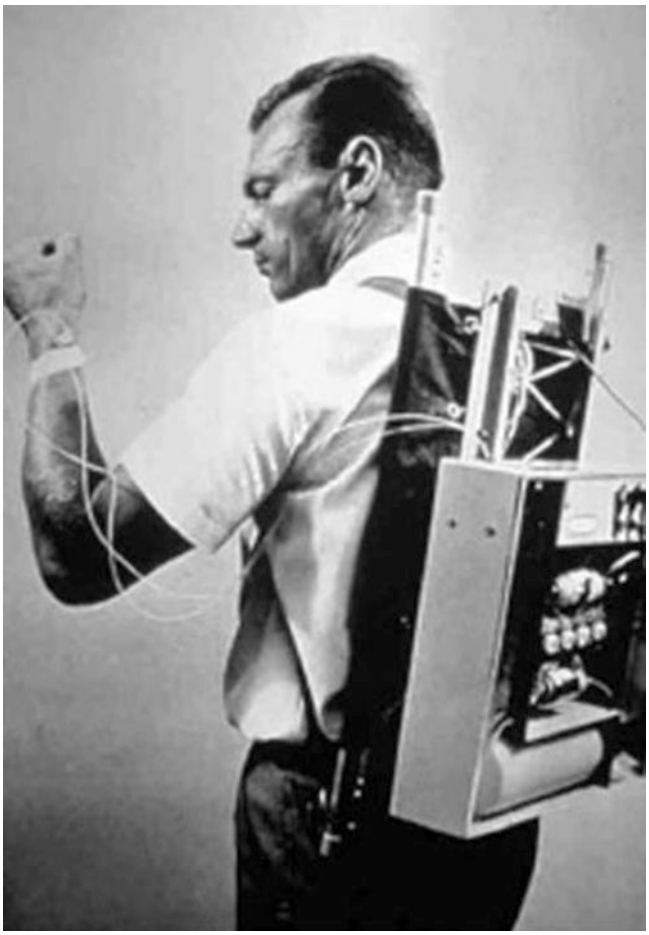


Fig. 69.7 Dr. Arnold Kadish with the first insulin pump

OmniPod (Insulet), T:Slim (Tandem), DANA R (SOOIL), Cellnovo, Accu-Chek Solo Micropump (Roche), and Ypsomed [56].

Medtronic introduced the first-ever "intelligent" insulin pump in 2003. The system comprises a MiniMed Paradigm 512 insulin pump and a Paradigm Link blood glucose monitor. Nowadays, BG readings from the glucometer are wirelessly and automatically transmitted to the insulin pump, and the required insulin doses are recommended by a Bolus Wizard calculator [57].

Insulin pumps are commonly used for insulin replacement in T1DM patients, but it has now been widely used by T2DM patients as well [58]. In patients with hyperglycemia, diabetes management with CSII provides better glycemic and metabolic control (reduces HbA1c, glycemic variation, and hypoglycemia) [59, 60]. The use of insulin pumps contributes to the patients' quality of life. However, the major limitations associated with the infusion sets are that they can exhibit handling issues and can detach, leak, or cause skin irritability, thus undermining the convenient use of insulin pumps [61]. Patient education before starting CSII therapy is of utmost importance to avoid the chances of a "pump failure" [62].

Patch Pumps

The barriers associated with infusion set have led to the development of "patch pumps." These pumps are free of infusion sets, small, lightweight, and attached to the skin through an adhesive. Patch pumps also offer additional comfort and flexibility to users, especially while traveling. Insulet introduced OmniPod, the first tubeless insulin pump in 2011. It consists of an integrated infusion set and automated inserter that converses wirelessly with an integrated BG meter. The Omnipod patch pump provides complete freedom to the users to engage in routine activities [63]. The specific simplified patch pump models available on the market are V-Go (Valeritas) and PAQ (CeQur) [64]. The second-generation Omnipod, which is smaller and more compact was launched in 2013. This version of the patch pump has modern features such as "human factor screens" and improvements in both correction and meal boluses for insulin dose calculation [65].

Continuous Intraperitoneal Insulin Infusion (CIPII)

Continuous intraperitoneal insulin infusion (CIPII) is considered to permit the infusion of insulin into the peritoneal cavity. The advantage of this method is that it more closely coincides the physiology than the other conventional therapies [66]. Two different technologies have been developed in CIPII: implanted intraperitoneal pumps such as MiniMed MIP2007C (Medtronic) and a percutaneous port attached to an external pump such as the Accu-Chek Diaport system (Roche Diabetes Care). The MIP 2007C is implanted under the subcutaneous tissue in the lower abdomen, and from this subcutaneous pocket, the peritoneum is opened, and the tip of the catheter is carefully inserted and directed towards the liver. After implantation, at least every 3 months the pump reservoir is refilled in the outpatient clinic with concentrated insulin transcutaneously. The Accu-Chek Diaport system permits insulin infusion into the peritoneal cavity through an Accu-Chek insulin pump and an infusion set. CIPII has been proven as a viable option for T1D patients with skin problems and unable to securely or efficiently control their diabetes with subcutaneous insulin [67].

The drawbacks of this route of insulin administration include the invasive nature, cannula blockage, higher cost, portal vein thrombosis, and peritoneal infection. Medtronic announced the worldwide termination of the implantable insulin pump in 2007.

Sensor-Augmented Pump Therapy (SAP)

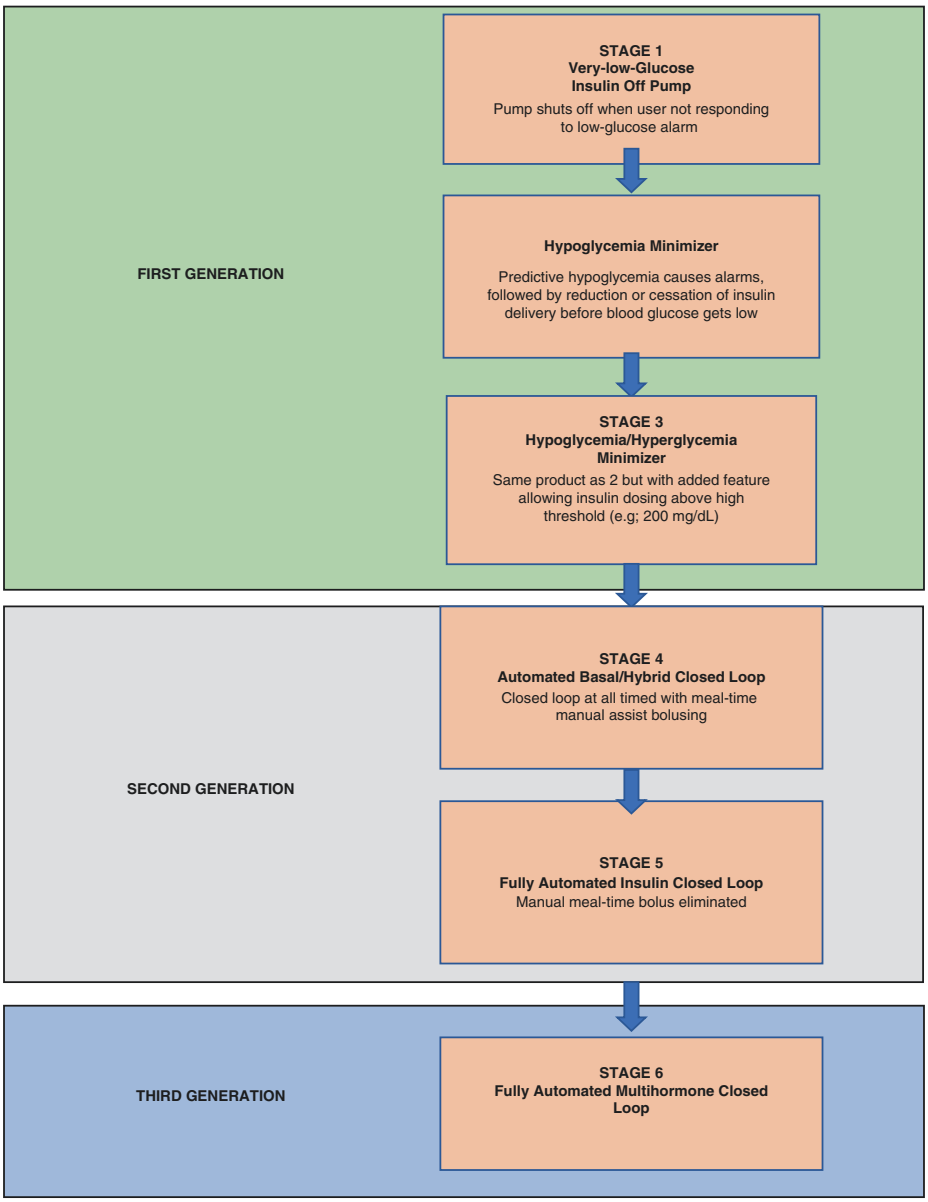
The new generations of CGMs are more accurate, smaller in size, and shown to improve glycemic control in patients with T1DM [68]. When CGM readings are used to adjust insulin

delivery through an insulin pump, it is known as sensor-augmented pump (SAP) therapy [69]. In patients with T1DM, SAP reduces A1c by 0.7–0.8% compared to baseline or MDI therapy. The introduction of real-time, sensor-augmented insulin pumps is considered a major turning point in the development of "closed-loop" insulin delivery or an artificial pancreas (AP) [1]. SAP therapy produces higher-level results in reducing hypoglycemia and achieving glycemic control to conventional therapies [70, 71].

Medtronic launched the MiniMed Veo System in 2009, with a Low-Glucose Suspend feature that automatically halts insulin delivery when sensor glucose levels reach a preset low threshold. This device has been considered the first stepping stone to an AP system [72].

The pump provides more accurate dosing, avoids the need for multiple daily injections, and thus provides convenience and a flexible lifestyle. They can also store a plethora of data that can be transmitted to computer programs or bolus insulin calculators and further analyzed to make insulin dose adjustments. The limitations of pump therapy are technical problems associated with the infusion set and higher acquisition costs. Patients also complained of skin irritations and infections at the insertion sites. Technical issues such as kinking, bending, or crimping of inserted cannulas and leakage of infusion sets have also been observed [61]. SAP requires patient involvement for using CGM glucose readings to adjust insulin pump delivery. This makes SAP susceptible to human errors.

Automation of Insulin Pump



Artificial Pancreas (Closed Loop)

MiniMed 530G with an Enlite sensor has been acknowledged as a first-generation artificial pancreas (AP) device system with Threshold Suspend automation. In 2013, this device was approved by the FDA for diabetes patients >16 years of age [55]. In 2015, Medtronic introduced the MiniMed 640G system, which has been taking one step closer to the artificial pancreas system. This system has integrated smart characteristics such as active insulin tracking, a bolus progress bar, and predictive battery life [73] (Fig. 69.8).

Since the conception of CSII, the main aim was to design an artificial pancreas that mimics exquisite sugar control with minimal human interference. An artificial pancreas or a "closed-loop" is a compilation of progressive technologies to engage automation to achieve glycemic targets. Generally, AP links three devices [74]:

1. A sensor like CGM that measures BG and sends data to a computer algorithm
2. A control algorithm to analyze the data and calculate the required insulin dose
3. An insulin infusion pump to deliver insulin as per the computer instructions

Fig. 69.8 A new-generation insulin pump: MiniMed 640G insulin pump system by Medtronic

Since 2016, safety and efficacy studies have been conducted on the combinational use of the predictive low-glucose suspension algorithm (PLGM) (commercially, "SmartGuard technology") with the MiniMed 640G insulin pump that automatically suspends insulin delivery based on the prediction of low glucose levels [75]. In 2017, the first hybrid closed-loop system, the MiniMed 670G insulin pump with a Guardian 3 sensor, was approved by the FDA (Fig. 69.9). When in auto mode, it functions as a hybrid closed-loop system that automatically controls basal insulin delivery every 5 min based on the CGM values to hold BG levels tightly to the specific target [8]. These systems have been reported to enhance glycemic targets [BG, HbA1c, time-in-range (TIR)] and reduce the incidence of nocturnal hypoglycemia to improve better safety, treatment satisfaction, sleep quality, and cognition in T1D patients [76–78].

In 2018, the FDA approved Insulet's Omnipod Dash System, a CSII system comprising a tubeless, waterproof, Bluetooth wireless technology pump with a capacity of 200 units of U-100 insulin and an advanced personal diabetes manager (PDM) that regulates the pump [79] (Fig. 69.10).

In 2021, Medtronic launched new MiniMed 780G insulin pump designed to work with Medtronic's Guardian sensors to continuously monitor glucose levels throughout the day (Fig. 69.11). Basal insulin adjusts insulin dosage every five minutes as needed based on glucose levels. Bolus is delivered automatically up to every 5 min if maximum auto basal delivery is reached or if glucose level is above 120 mg/dL. This pump helps to achieve the Time in Range goal of >70% and HbA1c goal of 7.0%.

Future steps in the evolution of the artificial pancreas will be [80]:

1. Use of predictive algorithms to minimize hypoglycemia even before hypoglycemia occurs.
2. Use of algorithms to keep blood sugar in target range (hypoglycemia/hyperglycemia minimizer).
3. Automated basal and/or hybrid closed-loop.
4. Fully automated (insulin).
5. Dual (insulin + glucagon) hormonal closed-loop.

Fig. 69.9 First Artificial Pancreas: MiniMed 670G insulin pump system with Guardian 3 sensor

Fig. 69.10 Omnipod DASH pump

Fig. 69.11 MiniMed 780G System

Alternate Controller-Enabled Infusion (ACE) Pumps

Another modern technology in this area has been the arrival of alternate controller-enabled (ACE) infusion pumps. Despite the conventional stand-alone pumps, ACE pumps can be interoperable: used jointly with different components of diabetes technologies, permitting custom-made diabetes management for patients according to individual device preferences. The ACE insulin pump can be combined with automated insulin dosing (AID) systems, CGMs, BG meters, and other electronics. In 2019, the FDA approved the first interoperable t:Slim X2 insulin pump for subcutaneous insulin delivery for children and adults with diabetes [81]. The FDA approved a new-generation, interoperable, control-IQ artificial pancreas system (tandem diabetes) in 2020. A clinical trial that revealed that the use of the control-IQ AP system was linked with a greater percentage of TIR, over the use of SAP, paved the way for this approval [78].

Do-It-Yourself Artificial Pancreas (DIY-APS)

People affected by T1DM have been expecting an affordable and efficient solution for the management of this chronic disease for decades. Lack of accessible and actionable data, unaffordability of the current systems, and long timeline of

medical device development cycles have led to general annoyance in the T1DM community. The first Diabetes Mine D-Data Exchange gathering at Stanford University spotlighted the sentiments and frustrations of patients with T1D and their families/caregivers gathered online under the hashtag "#WeAreNotWaiting" in waiting for their needs to be addressed in 2013. This event marked the beginning of the DIY-APS movement. A major dimension of the #WeAreNotWaiting initiative was that the tech-savvy diabetes followers started self-building their closed-loop systems, also known as "looping." These automated insulin delivery systems are generally known as a "Do-it-yourself" artificial pancreas (DIY-APS) [82, 83]. The basic components of DIY-APS are:

(a) A real-time CGM.
(b) An insulin pump.
(c) A minicomputer or smartphone app.

The diabetes community shared DIY diabetes device-related projects on digital and social media platforms such as Facebook, Twitter, NightScout, and GitHub, which led to the merging of these projects [84]. Through a gradual and systematic method of assembling, merging, and processing data from patients' devices to deliver significant actionable information, there has been a rush in the propagation and convergence of DIY diabetes device-related projects. Dana Lewis, Scott Leibrand, and Ben West launched the OpenAPS project, providing the instructions and outline of a DIY patient-built artificial pancreas system (APS) in 2014. In 2015, the open-source version, also known as OpenAPS, was launched [85]. On January 31, 2020, more than 1776 PWD around the globe have implemented various layouts of DIY-APS [86]. DIY-APS uses individually made unauthorized algorithms to convert CGM data and calculate insulin doses, FDA approved communication devices and insulin pumps. Since it involves the use of unauthorized algorithms, these systems are not FDA approved, commercialized, or regularized. In 2017, another innovation in the DIY-APS evolution was "RileyLink," designed by Pete Schwamb for his daughter Riley, who had T1D. It is a translator device that allows easy communication between the insulin pump and iPhone. This device is considered more user-friendly, and it is easy to set up and maintain procedures [87]. Real-life experiences from patients and caregivers, unscientific data, and published reports from selected cohorts have highlighted the clinical benefits and reductions in self-management burden with DIY-APS [88].

In India, Jazz Sethi, a 26-year-old professional dancer from Ahmedabad, who has been living with T1D since the age of 13, is the first user of Do-It-Yourself (DIY) artificial pancreas. *Diabetes and Metabolic Syndrome: Clinical Research and Review* has narrated her experience with this breakthrough technology, why she decided to use the system, and how the device has produced significant improvement in her quality of life and management of T1D [89].

There are mainly three types of DIY-APS:

1. OpenAPS
2. AndroidAPS
3. Loop

OpenAPS

OpenAPS is a safe, powerful, and easily understandable system that proposes to adjust insulin dosage to manage the BG levels in the recommended range, overnight and between meals. The first Open APS was developed by Dana Lewis, Scott Leibrand, and Ben West, and the code written with the help of Chris Hannemann was on a Raspberry Pi computer and a communication stick to connect to an old Medtronic pump.

Generally, an OpenAPS consists of an insulin pump, a CGM system, and an algorithm running on a microcomputer. The algorithms used in OpenAPS are oref0 (OpenAPS Reference Design Zero), Adjusting for unexpected BG deviation, and Bolus snooze. Recently, an "Advanced Meal Assist (AMA)" feature has been integrated into the OpenAPS algorithm. AMA gives an extremely adaptable algorithm for securely dosing insulin after meals, regardless of broadly differing meal types, and the high variations in rates of digestion between individuals, making it the most widely used postprandial insulin dosing algorithm. The ultimate aim of the OpenAPS system is to completely automate insulin dosing in all situations. In that regulation, an oref1 algorithm has been developed that utilizes small "supermicroboluses (SMB)" of insulin at mealtimes and ensures more rapid and secure insulin delivery in response to BG rises [90].

OpenAPS reads the CGM data every 5 min and queries the insulin pump every few minutes for recent settings and activities such as current and maximum basal rates, recent boluses, insulin on board (IOB), insulin sensitivity factor (ISF), carb ratio (CR), duration of insulin acting (DIA), and BG target/ range. Based on the communication from the insulin pump, OpenAPS updates the bolus wizard calculation and decides upon whether to cancel or supply a temporary basal. OpenAPS accomplishes this function through a physical piece of hardware called a "rig" that implement a sequence of commands to collect the CGM data, runs it through Oref0, and performs the dose calculations based on the pump setting values. The system can guide on changes in insulin to carbohydrate ratios and ISF settings through either Autosens (checking back 8–24 h) or Autotune (check back either 24 h or a user-specified period). However, this was the first developed system; recent users have been preferring AndroidAPS which offers more combinations of compatible devices and in-warranty pumps.

AndroidAPS

AndroidAPS is an open-source app with all properties of OpenAPS but runs on Google Android smartphones. The smartphone receives data from a CGM and transmits it with the insulin pump via Bluetooth. In 2017, the first AndroidAPS was developed in Europe by Milos Kozak and Adrian Tappe and it works with modern in-warranty pumps with Bluetooth capability. The algorithms used here are Oref0 and Oref1. The app is available in different versions particular to geographic locations and languages. The basic elements of the profile include basal rates (BR), ISF, CR, and DIA. AndroidAPS supplies multiple possibilities for remote monitoring of adults and pediatric patients with T1D. NSClient app can be used to check the relevant data by parents and caregivers of kids with T1D on their Android phones. Features like alarms using the xDrip+ app in follower mode, remote monitoring and control with SMS commands, and remote profile switch and temperature targets through the NSClient app provide the kid-friendly convenience of this system.

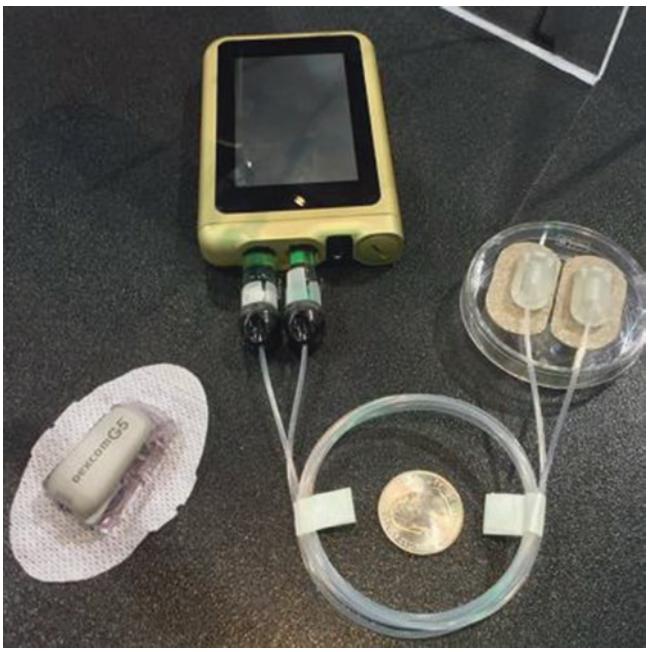


Fig. 69.12 iLet Bionic Pancreas

Loop

The Loop algorithm is different from OpenAPS and runs on an iOS operating system. The Apple iPhone receives CGM data and communicates with the insulin pump via Bluetooth. In 2016, the first loop was developed by Nate Racklyeft and a D-Dad, Pete Schwamb. Loop makes use of a free application, Xcode, to convert the raw code into an iOS application and install it on an iPhone. Loop documentation is available on GitHub and the builders need to register as Apple developers to install the necessary software. The loop makes a forecast using BG values every 5 min from 30 min ago and integrates between that value and the current glucose value to make adjustments in insulin dose and to provide bolus recommendations and temporary basal rates. The app communicates with a small translator device called RileyLink that ensures interaction between the pump, iPhone, and CGM [90]. It is almost the size of a tic-tac box and needs to be carried with you at all times. In a loop system, the pump speaks via radio language and the iPhone speaks via Bluetooth, and RileyLink acts as a translator to loop these parts together.

Bionic Pancreas (BP)

The "bionic pancreas" is a type of closed-loop system consisting of two infusion pumps (separately for insulin and glucagon) and connected to a CGM via a smartphone app. In 2015, the first bionic pancreas, "iLet" (Beta Bionics), exclusively for T1D treatment, was innovated by Dr. Edward Damiano. In this system, based on the appraised CGM data automated dosing assessments of insulin and glucagon levels are made every 5 min (Fig. 69.12). These data are transmitted to pumps to control insulin or glucagon delivery [91]. In 2019, the FDA approved iLet BP as the "breakthrough device designation" [92].

D-Dads

D-Dads are fathers whose fatherhood has been challenged by T1D. Unsatisfied with the disruption and unpredictability of diabetes care, some D-dads thought "outside the box" to ease the burden of diabetes management.

Dr. Edward R. Damiano, a professor of biomedical engineering at Boston University, was determined to develop a bionic pancreas when his 11-month-old son, David, was diagnosed with T1D. Frustrated with the absence of reliable technologies, he created a bionic pancreas with the help of physicians and researchers [93]. The US Food and Drug Administration (FDA) conferred "breakthrough device designation" to the iLet bionic pancreas in 2019 [94]. Pete Schwamb, a software engineer, made innovatory contributions in the field of diabetes technologies. Pete's effort to gain access to the insulin pump data of his 6-year-old daughter, Riley, led to the development of RileyLink, a translator device used to communicate between the insulin pump and iPhone. Later, he developed the first iOS-based automated insulin delivery system, "loop," in association with Nathan Racklyeft [95]. Bryan Mazlish, a Wall Street quantitative analyst and one of the cofounders of Bigfoot Biomedical, made a fully functional homebrew artificial pancreas to manage

his son's T1D. Being a hacker by profession, he has been recognized as a standard-bearer for the DIY-APS hacking mission [93]. Jeffrey Brewer, a past president of the Juvenile Diabetes Research Foundation (JDRF), also known as "the father of the artificial pancreas," has commenced research projects on automated insulin delivery systems. Later, he co-founded Bigfoot Biomedical accompanying Bryan Mazlish to develop its own closed-loop system, the Bigfoot smartloop system [96]. John Costik, the father of a 4-year-old boy, Evan, who had T1D, designed a code to hack his son's CGM, to upload the values into the cloud and remotely acquire those data using a web-based or android interface. He later made the code available as open-source and initiated "Nightscout CGM in the Cloud Project" for wider dissemination of the technology [85, 97]. Lane Desborough, D-Dad of Hayden is the name of an engineer from Medtronic, one of the so-called D-dads in diabetes technology by Nightscout CGM in the Cloud. He was a chief engineer at Medtronic and was one of the advocates of the #WeAreNotWaiting movement. Lane was the first person to get involved in the DIY-APS movement from the industry and later co-founded Bigfoot Biomedical [98]. Tidepool, a non-profitable organization was started by the D-Dads Howard Look and Steve McCanne and has been creating a regulated loop version of DIY-APS. Tidepool is currently on a venture to release a regulated version of the DIY-APS in collaboration with Omnipod and Dexco [99, 100].

D-Dads have been making significant contributions to turn the artificial pancreas dream into reality while focusing on its equitable access and affordability.

Bolus Calculator Apps

Bolus calculator/bolus advisor mobile apps are used for insulin dose calculation available in smartphones. These can function independently or can be integrated into pumps to calculate the accurate insulin dose by incorporating expected carbohydrate intake, measured blood glucose values, and previous insulin doses [101]. The most commonly used bolus calculator apps are Diabetes: M, mySugr (Roche), and PredictBGL. Bolus wizards are built-in automated bolus calculators specific to insulin pumps for insulin dose recommendations. The use of bolus wizards has been correlated with better glycemic control and treatment satisfaction [102]. In 2016, Endocrine Society Clinical Practice Guidelines have strongly promoted patients to use suitably adjusted built-in bolus calculators in CSII to improve glycemic control [103].

Implanted Pancreas

Another novel AP technology was the implanted artificial pancreas, a fully implantable insulin delivery device, which is under development at De Montfort University. It is a gel-based system that responds to BG variation by changing the insulin delivery rate. The performance of this system in glycemic control is well tested in a diabetic domestic pig [104]. It reduces hourly management and human interference to improve user acceptance and quality of life in diabetes patients [105].

Insulin Inhalers

Insulin delivery to the lungs was the first reported substitute for subcutaneous injection. It has long been estimated that insulin delivery by aerosol reduces blood glucose [106]. Insulin inhalers permit patients to breathe fine-inhalable insulin (pulmonary insulin) (either dry powder-based formulations or solution) into their lungs [12].

Advantages of the pulmonary route include a broad and well-perfused absorptive surface, the absence of certain peptidases that are present in the gastrointestinal (GI) tract that breaks down insulin, and the ability to bypass the "first-pass metabolism" [107]. Although the exact mechanism of insulin absorption across the pulmonary epithelium remains unclear, it is believed to involve transcytotic and paracellular mechanisms [106].

When introduced to the market, inhalable insulin was considered a remarkable innovation to address needle phobia and incorrect insulin injection techniques pertained to systemic insulin delivery methods [108]. In 2006, the first inhaled product Exubera® was approved by the US FDA. Exubera® was a dry power formulation available as 1 mg and 3 mg doses to be taken with the help of an Inhance™ inhaler device [109]. Exubera® was found to have pharmacokinetic and pharmacodynamic (PK/PD) properties similar to insulin aspart with a faster onset of action (10–15 min) [110]. In clinical trials in patients with uncontrolled T1DM and T2DM, Exubera® was found to reduce postprandial blood glucose and A1c markedly [111] although Exubera® was contraindicated in smokers as it increased the risk of hypoglycemia due to greater absorption compared to nonsmokers [112]. Along with this, patients were required to undergo pulmonary function tests before treatment initiation, after 6 months, and annually thereafter [109, 112]. This product did not flourish well commercially despite the noninvasive route possibly due to higher cost, the bulky delivery device, concerns related to decline in pulmonary function, and less preference by the patients and physicians. In 2007, this product was withdrawn from the market due to poor sales volume.

Another promising inhaled insulin is Afrezza (Sanofi and MannKind) based on Technosphere® dry powdered formulation. The onset of action of Afrezza inhaled insulin is 15 min and duration is 2–3 h, which is ideal for postprandial blood glucose control [113]. Initially, the common side effects are transient non-productive cough and a modest

reduction in lung function [114]. In 2014, Afrezza got FDA approval for prandial insulin therapy [115]. The delivery system of Afrezza is small, handy, and displays the dose in units [116]. The use of Afrezza has provided remarkable glycemic control and reduction of hypoglycemia in T1DM patients [117, 118]. The recognition of inhalable insulins is further limited by insurance barriers, safety concerns, and competing products [116].

Jet Injectors

Another possible innovation to the market could be jet injectors, a type of syringe that dispenses insulin subcutaneously with the use of a high-pressure air mechanism. In the 1860s, Pioneer jet injector technology was introduced. Later, it was reintroduced in the 1940s as the "Hypospray," focusing on patients' self-management of insulin. In the 1950s, the US military designed a high-speed system, "Ped-O-Jet" (Keystone Industries), in the category of a multiuse nozzle jet injector (MUNJI) for mass vaccination programs. In 1997, the Ped-O-Jet was discontinued as a result of contamination issues built with the use of MUNJI [119]. During the 1990s, the new-generation, disposable-syringe jet injectors (DSJIs) with disposable dose chambers (insulin cartridge) and nozzles were launched. Even though the idea is not firsthand to the market, the wider acceptance of these devices has been interrupted by the cost, low absorption with the repeated use, and high contamination rates of the previous systems [120]. The jet injectors are a solution for patients with needle phobia [121]. Recent safety and feasibility studies have assessed the treatment efficiency and pharmacokinetic and pharmacodynamic (PK-PD) profiles of the insulin administered by the new-generation jet injectors [122].

Oral Insulin

The oral route of insulin administration may be the most patient-friendly way of taking insulin and it could more closely imitate physiological insulin delivery (more portal insulin concentration than peripheral) [123]. Despite this, the limitations in making oral insulin include inactivation by proteolytic enzymes in the GI tract and low permeability through the intestinal membrane due to the larger size and hydrophobicity of insulin resulting in poor bioavailability. Several pharmaceutical companies are engaged in developing carriers to protect insulin from GI degradation and facilitate intestinal transport of insulin to deliver insulin to the circulation with sufficient bioavailability.

Natural and synthetic nanoparticles have been used as a carrier or vehicle for insulin such as chitosan, liposomes, polymeric nanovesicles, polylactides, poly-ε, poly-alkyl cyanoacrylate, and various polymeric hydrogels [124–129].

Certain oral insulin preparations such as Capsulin, ORMD-0801, IN-105, oral hepatic directed vesicles, and Eligen have undergone phase 1 and phase 2 trials with promising results [130].

Colonic Insulin Delivery

Oral colon delivery is currently considered of importance not only for the treatment of local pathologies, such as primarily inflammatory bowel disease but also as a means of achieving systemic therapeutic goals. The large intestine is preferably not suited for absorption processes for drugs but it has certain advantages over the small intestine like long transit time, lower levels of peptidases (prevent the destruction of peptides), and higher responsiveness to permeation enhancers. Accordingly, it has been under extensive inquisition as a possible strategy to enhance the oral bioavailability of peptide and protein drugs. Oral delivery systems intended for colonic release of insulin were devised according to microflora-, pH-, and time-dependent strategies [131].

Bioavailability and pharmacological availability data are generally still far from being reliable in terms of magnitude, onset, duration, and above all, consistency for this route of administration and it is under investigation and despite its progress, there is still a long way to go before these products will be available on the market.

Nasal Insulin

In theory, intranasal delivery has several advantages over oral (bypass GI peptidases), subcutaneous (noninvasive and painless), and inhalation route (no issue with lung function) which makes this route appealing for the delivery of insulin. However, intranasal delivery has disadvantages such as limited permeability of a large molecule through the nasal mucosa and rapid mucociliary clearance resulting in variable absorption [132].

Significantly, intranasal delivery with early porcine and bovine insulins was studied in patients with T1DM [133, 134]. Currently, two technologies are under investigation: Nasulin™ (CPEX Pharmaceuticals) and nasal insulin by Nastech Pharmaceutical Company Inc. Both insulin preparations have a bioavailability of about 15–25% with the onset of action approximately 10–20 min [135, 136]. The substances such as bile salt, surfactant, and fatty acid derivatives are being investigated to improve mucosal permeability of insulin but they increase the risks for local irritation, nasal secretion, sneezing, or burning sensation [137].

Nasal insulin crosses the blood-brain barrier since it has a hypothesized effect on memory function [138]. Treatment with intranasal insulin improved memory, preserved caregiver-rated functional ability, and preserved general cog-

nition without any remarkable hypoglycemic event. These improvements in cognitive functions were combined with changes in the Aβ42 level and in the tau protein-to-Aβ42 ratio in cerebrospinal fluid [139]. Based on these, investigations are ongoing to evaluate the usefulness of this agent for the treatment of Alzheimer's disease.

Buccal Insulin

Buccal delivery of insulin has similar efficacy as oral insulin with the advantage of bypassing GI degradation. In addition, the relatively large surface area results in better bioavailability [140]. Initially, Generex Biotechnology developed Oral-lyn™ which is a liquid formulation of short acting insulin that is administered using Generex's metered dosage aerosol applicator (RapidMist™). Eli Lilly and Generex conducted phase 1 and phase 2 trials in patients with T1DM and T2DM with favorable results [141]. Another fragment being developed by Shreya Life Sciences Pvt. Ltd., India, is oral Recosulin® [142].

Another technique for the delivery of insulin is fast dissolving films as a substitute to oral tablets for rapid drug delivery [143]. The Monosol Rx (Pharm Film Drug delivery technology) in collaboration with Midatech Company developed Midaform™ insulin, which is delivered by buccal route.

Transdermal

Transdermal insulin delivery terminates the problems associated with needles and injections and the large surface area of the skin makes it an appropriate route for insulin delivery. Although the perforation of insulin is halted by the stratum corneum, the outermost layer of the skin, numerous methods have been explored to overcome the barrier of the stratum corneum [144].

There are several strategies insulin can be delivered transdermally such as:

(a) Iontophoresis, the technique that uses small electric currents [145].
(b) Sonophereis or phonopheresis uses ultrasound waves [146].
(c) Microdermal ablation by removing the stratum corneum [147].
(d) Electroporation utilizes high voltage pulses that are applied for a very short time [148].
(e) Transfersulin is the insulin encapsulated in transferosome, an elastic, flexible vesicle, which squeezes by itself to deliver drugs through skin pores [149].
(f) Insupatch™, a device developed as an add-on to an insulin pump that applies local heat to the skin in order to increase the absorption of insulin [150].
(g) Recombinant human hyaluronidase (rHuPH20) to increase insulin absorption from subcutaneous tissue [151].

Moreover, microneedles with a 1 μm diameter and of various lengths can deliver insulin in an effective, accurate, and precise manner [152]. Microneedle technology also can be combined as a transdermal patch.

The transdermal insulin delivery techniques are limited by skin injury, burn or blister formation, and rarely significant pain and discomfort.

Other Non-conventional Routes

Ocular Route

No human trial has been reported with this route and an animal study failed to achieve significant plasma insulin concentration [153].

Rectal Route

Rectal gels [154] and suppositories [155] showed fair results. However, this route is not commercially viable.

Intra-Tracheal

In 1924, the administration of insulin was reported [156] but is not practical so not taken up for further development.

Conclusion

There is a long history of research focusing on recognizing a route of administration for insulin that is minimally or non-invasive, effective, safe, convenient, and cost-effective for patients. Each route and delivery method has its own potential advantages and disadvantages. There has been a high-speed evolution in diabetes technologies to improve the quality of life and to extend the endurance of subjects with diabetes. Though there were commendable developments in the currently available devices, many of those were prohibitively expensive. Additionally, there were serious issues associated with cannula blockages, infusion set handling, Bluetooth connectivity, and user-friendliness. As the search for more accurate and user-friendly methods continues, advances in pumps, CGMs, and predictive algorithms can

make the closed-loop system as physiologic as possible with >90–95% TIR and the least time spent in hypoglycemia. Some of the promising experiences are shared by subjects using DIY-APS. The DIY revolution has prompted all device manufacturers to introduce ACE pumps and compatible sensors. The ultimate dream is to develop an artificial pancreas capable of 100% TIR and 0% time below range and affordable to everyone. Even though the mission demands enormous commitment and time, it has the potential to transform diabetes therapy.

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