Chapter 1
Overview of Type 2 Diabetes

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1.1 Epidemiology and Global Disease Burden

Diabetes is a serious and escalating global health problem. The global prevalence is 8.3 % and 387 million people are currently affected [1]. Over 45 % of people with type 2 diabetes are undiagnosed and the total number affected is predicted to rise to 592 million by 2035. An additional 316 million people are estimated to have impaired glucose tolerance and many of these will progress to type 2 diabetes. For example, in the UK the prevalence of diabetes is 6.0 %, affecting 3.2 million people, while in the USA the prevalence is 12 % of the population.

The causes of this epidemic are multifactorial including aging populations, rapid cultural and social changes (e.g., increased urbanization, dietary changes), physical inactivity, and excess body weight. For example, in Scotland, over 50 % of patients with type 2 diabetes are obese and a further 30 % are overweight, indicating that weight loss should be a priority in both prevention and treatment [2]. Prevalence rates are higher in elderly patients (approximately 15 % affected), with nearly 60 % of patients with type 2 diabetes over the

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age of 65 years [2]. This has associated management challenges as elderly patients often have multiple comorbidities, increased risks of adverse drug effects and hypoglycemia, and additional health and social care support requirements.

Increasing numbers of younger obese and overweight patients are being diagnosed, which brings concerns of the long-term effects of increased risk of developing diabetes- and treatment-related complications. Complications such as renal failure and amputations are a major cause of disability, reduced quality of life, and death. Early disability in patients under 60 years of age causes loss of productivity and earning potential, affecting individuals along with their families, communities, and economies. Cardiovascular disease (CVD) is a leading cause of death in this population and 50 % of diabetes-related deaths occur in patients under 60 years of age [1].

Thus, tackling diabetes is one of the most challenging health problems of the 21st century. International Diabetes Federation data from 2014 shows the serious global impact of diabetes (Fig. 1.1). Almost 80 % of people with diabetes live in low and middle income countries, and these countries suffer a disproportionate burden in terms of prevalence, morbidity, mortality, and economic consequences. Health and social care systems are struggling to manage this burden of increasing medical and social care needs. Globally, $612 billion USD is spent annually on diabetes care, which represents 11 % of worldwide healthcare expenditure [1]. Internationally, there is a large disparity in health care spending; North America and Caribbean countries alone spend $310 billion (51 % of the total worldwide expenditure). Despite this high level of spending, these countries still have a death rate of 41 % in patients under 60 years of age. Overall, nations in the Western Pacific have the highest diabetes burden, with 138 million people affected (approximately 35 % of the global patient population) but only $101 billion USD spent (16 % global expenditure) [1].

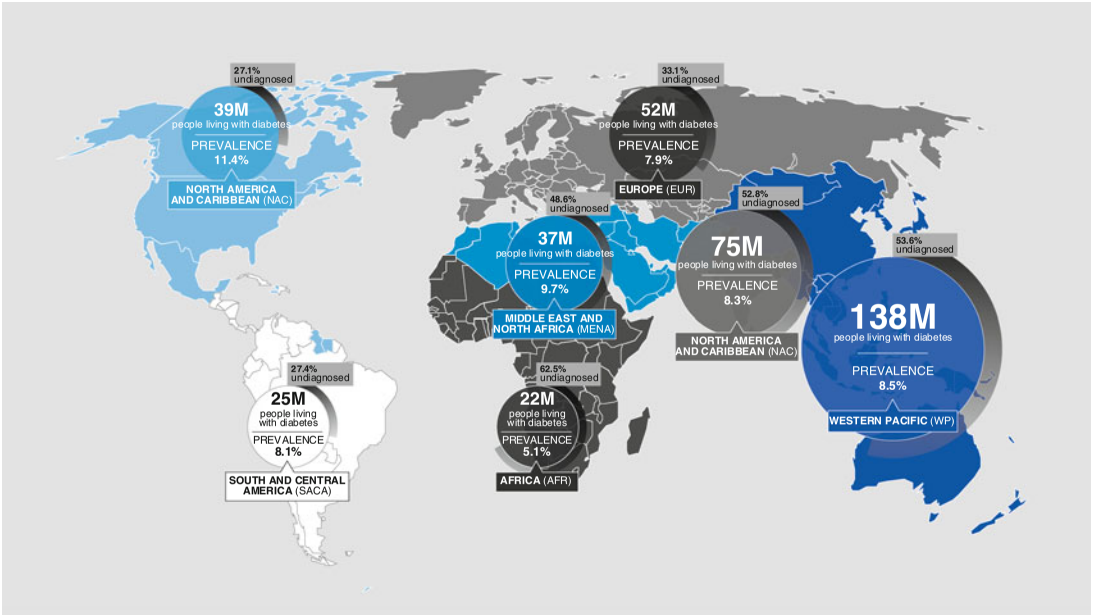

FIGURE 1.1 Global prevalence of diabetes (Reproduced with permission from the International Diabetes Federation [1] ©IDF)

1.2 Diagnostic Criteria for Diabetes

The diagnostic criteria from the World Health Organization (WHO) and the American Diabetes Association (ADA) are shown in Table 1.1 [3, 4]. Glycated hemoglobin (HbA1c) concentration of ≥48 mmol/mol (6.5 %) can be used for the diagnosis of diabetes. Patients without symptoms of hyperglycemia require two different tests (e.g., fasting plasma glucose and HbA1c) with concordant results or repeat testing on another day for confirmation.

Table 1.1 Diagnostic criteria for diabetes

	Impaired fasting glucose and impaired glucose tolerance (WHO/IDF)	**Prediabetes (ADA)**	**Diabetes mellitus (WHO/IDF and ADA)**
HbA1c (%)	–	5.7–6.4 % (39–48 mmol/mol)	≥6.5 % (48 mmol/mol)
Fasting plasma glucose (mmol/L)	6.1–6.9	5.6–6.9	≥7.0
OGTT 2-h plasma glucose (mmol/L)	7.8–11.0	7.8–11.0	≥11.1
Random glucose (mmol/L)	–	–	≥11.1 with classic symptoms

ADA American Diabetes Association, *HbA1c* glycated hemoglobin, *IDF* International Diabetes Federation, *OGTT* oral glucose tolerance test, *WHO* World Health Organization

The WHO define impaired glucose tolerance as a 2-h blood glucose between 7.8 and 11.0 mmol/L on oral glucose tolerance test (OGTT); "impaired fasting glucose" is defined as fasting plasma glucose between 6.1 and 6.9 mmol/L. ADA criteria describe a diagnosis of "prediabetes" in which glucose tolerance, fasting glucose, or both are impaired. This also includes patients with HbA1c 39–46 mmol/mol (5.7–6.4 %). These conditions are associated with increased risk of type 2 diabetes and cardiovascular disease. Figure 1.2 illustrates the natural history of impaired glucose tolerance progressing into type 2 diabetes and the mechanisms involved [5, 6]. Approximately 25 % of people will develop diabetes within 5 years and, while lifestyle interventions can reduce the risk of disease progression, there is no international consensus regarding screening and therapies for patients with prediabetes.

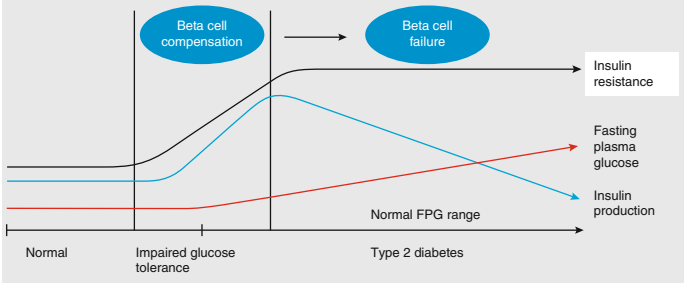

FIGURE 1.2 The natural history of type 2 diabetes. The key aspects in developing type 2 diabetes are insulin resistance, decreased insulin production, and increased blood glucose. With impaired glucose tolerance, beta cell compensation occurs, caused by loss of beta cell sensitivity to glucose and progressive beta cell failure. This contributes to delayed insulin secretion in response to oral glucose. *FPG* fasting plasma glucose (Adapted from Bailey [5] and DeFronzo and Ferrannini [6])

1.3 Glucose Homeostasis

Glucose homeostasis is normally maintained by a balance between glucose entering the bloodstream from intestinal absorption and hepatic glucose production, versus the uptake and metabolism of glucose by peripheral tissues. In the prandial state, pancreatic β-cells are stimulated to secrete insulin and glucagon secretion from alpha cells is reduced. This causes increased glucose uptake into insulin sensitive tissues namely heart, skeletal muscle, and adipose tissue. Hepatic glucose production is reduced and anabolic metabolism is promoted. In the fasting state, insulin levels are reduced and glucagon secretion is increased. Hepatic glucose production through glycogenolysis and gluconeogenesis maintains glucose levels.

The kidneys maintain homeostasis throughout by filtering and reabsorbing all glucose ensuring that no glucose is lost in the urine. 90 % of filtered glucose is reabsorbed by the high capacity sodium-glucose linked transporter 2 (SGLT2) in the convoluted segment of the proximal tubule [7]. The remaining 10 % is reabsorbed by the SGLT1 transporter in the straight arm of the descending proximal tubule.

1.4 Pathogenesis of Type 2 Diabetes

Type 2 diabetes is a complex heterogeneous disorder characterized by pancreatic β-cell dysfunction and insulin resistance. The relative contribution of each factor varies between individuals. Insulin resistance in muscle is usually the first abnormality detected [8]. Initially this signals β-cells to produce more insulin to maintain glucose homeostasis [9]. However, progressive β-cell dysfunction develops with loss of pulsatility of insulin secretion, abnormal insulin formation, loss of sensitivity to glucose stimulation, and delayed insulin secretion. β-cell loss accompanies β-cell failure and insulin production becomes inadequate, resulting in hyperglycemia. Hyperglycemia itself contributes to further β-cell dysfunction and a vicious cycle occurs. Insulin resistance is well established

when impaired glucose tolerance develops (Fig. 1.2) and further decline in β-cell function leads to the development of type 2 diabetes.

The neurohumoral feedback mechanisms between β-cells and insulin sensitive tissues (heart, skeletal muscle, and adipose tissue) are not fully understood so the precise mechanism by which insulin resistance causes β-cell failure remains unknown [9]. Obesity is a major cause of insulin resistance and is associated with inflammation of adipose tissues and excess fatty acid secretion, also known as lipotoxicity which causes β-cell dysfunction. Other pathophysiological mechanisms contributing to β-cell dysfunction are islet amyloid deposition and the lack of ability to regenerate β-cells in adults [10, 11].

Figure 1.3 illustrates the multiple pathogenic processes contributing to hyperglycemia [7]. Hepatic glucose production is increased, skeletal muscle glucose uptake is reduced, and glucagon secretion is increased. Incretins (glucagon-like

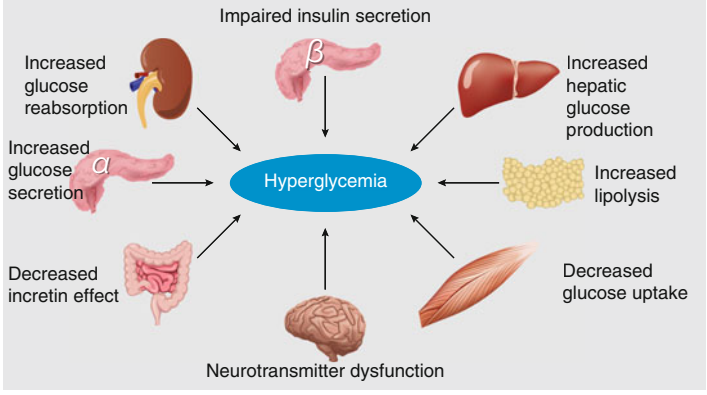

Figure 1.3 Multiple pathological features contribute to hyperglycemia in type 2 diabetes ("ominous octet" model). Skeletal muscle, liver, and pancreas, the fat cell, gastrointestinal tract, kidney, and brain all play important roles in the development of glucose intolerance in individuals with type 2 diabetes mellitus. All of these represent targets for drug therapies (available and potential drugs in development) (Adapted from DeFronzo [7])

peptide [GLP-1] and gastric inhibitory polypeptide [GIP]) are insulin secretagogues released from intestinal cells in response to feeding. In type 2 diabetes, there is impaired release of incretins, which may be a secondary process rather than primary abnormality. Additionally, in the kidneys there are increased levels of SGLT2 receptors in patients with diabetes, causing increased glucose reabsorption. Normal homeostatic control is lost as increased glucose levels are absorbed into the blood and excess glucose is excreted into the urine. Gluconeogenesis in the renal cortex may further contribute to hyperglycemia [12]. There is also evidence of central neurotransmitter dysfunction with studies showing reduced inhibition within hypothalamic appetite regulation centers [7]. Research aiming to get a better understanding of the various mechanisms causing hyperglycemia and how they interact will potentially aid the identification of suitable therapeutic targets for drug development.

1.5 Risk Factors for the Development of Diabetes

Type 2 diabetes is a heterogeneous disorder involving interaction between genetic and environmental factors. Genetic susceptibility results from complex polygenic risk factors as opposed to monogenic causes which are only responsible for 1–2 % of diabetes cases. Over 50 genetic loci have been discovered to be associated with increased risk of type 2 diabetes and most of these are linked to defects in β-cell function [9]. Approximately 40 % of patients have at least one parent with type 2 diabetes and monogenic twin studies have reported up to 90 % concordance [13, 14].

People with Asian, Pacific Islander, and Afro-Caribbean ethnicity have the highest risk of developing type 2 diabetes. The importance of environmental factors interacting with genetic factors is shown by the varying prevalence across geographical areas. For example, Pima Indians living in USA have up to a five-fold greater risk than Pima Indians living in Mexico [15].

Table 1.2 Risk factors for type 2 diabetes

Non-modifiable risk factors	Modifiable risk factors
Age >45 years	Obesity
Family history	Sedentary lifestyle
Ethnicity	Dietary factors
History of gestational diabetes	Smoking
	Previously identified glucose intolerance
	Dyslipidemia
	Hypertension

The other risk factors for type 2 diabetes are listed in Table 1.2. Excess calories and high energy diets are a central causal mechanism of obesity and type 2 diabetes. Type 2 diabetes is more prevalent in people over 65 years and aging populations are a major contributing factor to increasing prevalence of type 2 diabetes.

1.6 Clinical Features of Diabetes

Type 2 diabetes is the commonest cause of diabetes in adults. Many patients are asymptomatic at diagnosis and hyperglycemia is detected on routine or screening blood tests. The classic symptoms of hyperglycemia are polyuria, polydipsia, nocturia, blurred vision and, less frequently, weight loss. Many patients describe symptoms retrospectively following diagnosis. Glycosuria causes an osmotic diuresis and dehydration, and patients who take sugary drinks as replacement can exacerbate hyperglycemia and the osmotic diuresis. Hyperglycemia is associated with increased risks of infection and patients can present with isolated or recurrent infections, commonly urinary tract infections, genital thrush, and/or cellulitis.

Rarely patients present with hyperglycemic hyperosmolar state (HHS) characterized by severe hyperglycemia, dehydration, and reduced consciousness. This is more common in elderly patients and is often associated with sepsis, myocardial infarction, or other intercurrent illnesses. Diabetic ketoacidosis (DKA) classically occurs in type 1 diabetes but this can also occur in a small cohort of patients with type 2 diabetes with severe β-cell dysfunction. This group is called 'ketosis-prone diabetes' and it usually only occurs under certain circumstances such as severe sepsis or illness. Patients will require insulin treatment following DKA, but the clinical course is variable and in the longer term they may achieve insulin independence.

1.7 Complications of Diabetes

Chronic hyperglycemia causes microvascular and macrovascular complications which are the major cause of morbidity and mortality. The UK Prospective Diabetes Study (UKPDS) showed the importance of good glycemic control to reduce the risk of microvascular complications [16]. Several other factors including hypertension, dyslipidemia, and metabolic syndrome contribute to the risk of developing complications, and therapeutic management to reduce these factors is a priority of diabetes care. Cardiovascular disease, primarily myocardial infarction and stroke, is the most common cause of mortality in patients with diabetes.

Diabetic retinopathy is the most common complication, affecting approximately 40 % of patients and is a major cause of blindness. Cataracts are more common in diabetes and another cause of visual impairment.

Diabetic nephropathy is a leading cause of kidney failure. Onset typically starts with microalbuminuria, progressing to macroalbuminuria and decline in renal function/estimated glomerular filtration rate. Eventually, renal replacement therapy with dialysis and/or transplant may be required.

Diabetic foot disease is one of the most feared complications due to peripheral neuropathy and/or ischemia and has a high risk of amputation. Other neuropathic complications

are autonomic neuropathy (causing gastroparesis), postural hypotension, diarrhea, and erectile dysfunction.

Furthermore, there are risks of complications and adverse effects due to treatments for diabetes. Hypoglycemia is the most common and serious of these and can lead to severe episodes causing seizures, coma, or even death.

Key Points

- Type 2 diabetes is a major global health problem affecting 387 million people worldwide, and of these 45 % are undiagnosed.
- Diagnostic criteria for diabetes include measurement of random or fasting blood glucose concentrations, and/or HbA1c.
- Type 2 diabetes is a heterogeneous disorder characterized by pancreatic β-cell dysfunction and insulin resistance. The relative contribution of each factor varies between individuals.
- There are identifiable risk factors for the development of diabetes, including increased weight and reduced physical activity, aging, as well as genetic and ethnic factors.
- Diabetes is a common cause of morbidity and mortality. Microvascular complications can lead to blindness, renal failure, and amputation. Macrovascular complications can cause coronary heart disease, stroke, heart failure, and premature death.

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