Introduction, Demographics, and Epidemiology of Diabetes

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Introduction

Diabetes mellitus (DM, diabetes) is a condition caused by an inability of the insulin produced by the pancreas to adequately transfer glucose into cells via transporter recruitment. Depending on insulin secretion or lack thereof, the resultant transporter recruitment may be amplified or reversed, leading to uncontrolled hyperglycemia. The condition increases the risk of developing other comorbidities and complications, including hypertension, cardiovascular disease, cerebrovascular accident (CVA), skin infections and diseases, nephropathy, retinopathy and other ocular diseases, mental health status changes (e.g., depression, anxiety), neuropathy, and lower-limb compromise [1]. Diabetes is also implicated as the seventh leading cause and a contributing factor in mortality, with the condition recorded on 234,051 death certificates in the United States in 2010 [1].

The most common classifications of diabetes mellitus are polygenic forms Type I (T1DM) and Type II (T2DM). Type I is characterized by an absence of insulin production, due to autoimmune destruction of pancreatic beta cells, and may be immune-mediated or idiopathic. Type II is an acquired condition in which the pancreas either becomes insulin deficient or sufficient insulin is produced but cannot be effectively used, termed insulin resistance. More than 90 % of all diabetes diagnoses are of T2DM [2]. A subset of T2DM diabetes is gestational diabetes (GDM), which may present during the second or third trimesters of pregnancy and often persists after pregnancy.

In 2012, the American Diabetes Association (ADA) estimated economic costs of diabetes including hospital or emergency care, clinic visits, and medication, to approach $245 billion. This is an increase of $71 million (41 %) over a five-year period, in the United States and $548 billion globally [3–5]. Additionally, indirect costs, due to decreased productivity, disability, and premature mortality, were estimated at $69 billion in the United States. The National Diabetes Statistic Report (NDSR) concluded that medical expenses of diabetic patients are 2.3 times more than expenses of nondiabetic patients [4].

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Demographics

When categorizing countries into seven geographic regions (i.e., Africa, Middle East/North Africa, South East Asia, South/Central America, Western Pacific, Europe, North America/Caribbean), the International Diabetes Federation (IDF) estimated that the highest rates of prevalence of DM will be in Africa (93 %), the Middle East/North Africa (85 %) and South East Asia (64 %) by the year 2035 [5]. The IDF report has also defined the international cost of diabetes as 11 % of total healthcare expenses (i.e., expenses by health systems and patients), as approximating $612 billion. This expenditure is expected to increase to about $627 billion by 2035 [5].

An increased risk of DM has been linked to numerous demographic factors, including age, sex, race/ethnicity, socioeconomic/employment status, and environment/location. Although these factors have been reported to increase the risk of developing DM, it may be difficult to explain how their interactions lead to DM since at times no specific cause and effect may be found.

Age

The risk of developing DM appears to increase as patients get older. The Centers for Disease Control (CDC) has reported the incidence of DM (per 1000 people) between 1980 and 2011 in the United States (Table 1.1). For patients 18–44 years of age it reported a peak of 4.3 cases (per 1000 people) in 2008 and 2009 (tied). Within this age group there were 23,525 new cases of DM, 18,436 diagnosed as T1DM and 5089 as T2DM, in patients under 20 years of age. By 2014, the NDSR estimated 208,000 cases of DM had been diagnosed in Americans under 20 years of age, or about 0.25 % of that age cohort. The 45–64 age cohort showed a peak of 14.3 newly diagnosed cases (per 1000) in 2008, while patients 65–79 years of age had a peak incidence of 15.4 cases in 2011 with a 31-year average of 10.2 cases per 1000 people. In addition, it also reported that in patients greater than 65 years of age, the prevalence of diagnosed and undiagnosed diabetes approached 11.8 million, or 25.9 % for that age demographic [10].

Table 1.1 Incidence (per 1000 people in age cohort) of newly diagnosed diabetes cases

Age cohort	1980 (first year)	2011 (most recent year)	31-year average	Range (year)
18–44	1.7	3.3	2.5	1.4 (1985)–4.3 (2008, 2009)
45–64	5.2	11.9	8.9	4.6 (1991)–14.3 (2008)
65–79	6.9	15.4	10.2	5.1 (1989)–15.4 (2011)

Sex

The CDC also discussed the incidence of DM sorted by patient sex. In the female population, the incidence of newly diagnosed cases ranged between 2.8 (1988) and 5.9 (2011), with a 31-year average of 3.9 cases (per 1000 females per year). The male population showed similar data, with the incidence of new cases ranging between 2.6 (1981) and 7.0 (2010) (per 1000 males per year) with a 31-year average of 4.1 cases [6]. This indicates that since 1988 there appears to be an overall increase in the development of DM in both sexes.

Race/Ethnicity

In the United States, the rate of diabetes diagnoses were found to be the greatest in the adult American Indian and Native Alaskan populations, with an incidence of 15.9 % (per 1000) in 2014. For other races, the reported rates of diabetes diagnoses were 13.2 % for non-Hispanic blacks, 12.8 % for Hispanics, 9.0 % for Asian Americans, and 7.6 % in non-Hispanic whites. Within this subgroup of the Asian American population, the largest rates of diagnoses were identified in Asian Indians (13.0 %) and Filipinos

(11.3 %). A study of six Asian ethnic groups residing in California showed a higher prevalence of T2DM in second-generation Asian Chinese and Filipino men, and in first-generation Asian Filipino women and Korean women, compared to a Caucasian/White cohort [7]. In the Hispanic subgroup population, Puerto Ricans (14.8 %) and Mexican Americans (13.9 %) were identified as having the greatest rates of diabetes diagnoses [1].

The large differences, in prevalence of diabetes between various racial/ethnic groups, highlight environmental and genetic risk factors [8, 9]. Patterns of increased prevalence of diabetes have been established for ethnic groups migrating from rural/agricultural environments to urban or Westernized settings; however, any geographic location adjustment, not necessarily from rural to urban, has also shown an increase in prevalence [9]. For instance, second- and third-generation Japanese Americans, whose ancestors migrated to the Seattle, Washington area, demonstrated increased rates of diabetes (16–20 %) compared to the native Japanese population (4–5 %) for both sexes [10, 11]. Genetically, the Japanese population has shown a propensity for beta cell dysfunction, specifically Fujimoto et al. defined an association between the −30 beta cell GCK gene promoter, beta cell dysfunction, and abnormal glucose tolerance as well as other gene variants related to beta cell dysfunction. Combining environmental factors, such as increased caloric diet and decreased physical activity leading to obesity, in this genetically vulnerable population may ultimately lead to increased rates of diabetes, especially if these modifiable disease influencers are unchecked [11].

Other ethnic groups have also shown a similar genetic susceptibility to diabetes, including Mexican Americans, Latinos, African Americans, American Indians, and Pacific Islanders [8]. Epigenetic- and gene-based research has associated the rs10811661 T allele to T2DM in both Asian and European ethnicity groups [12]. Additionally, a study of eastern Asian Indian T2DM patients and controls found a significant relationship between the haplotype of two risk alleles of two genes, PON1 and PON2, in T2DM patients. PON1 and PON2 belong to a multigene family related to oxidative activities on chromosome 7 [13]. Therefore, for many ethnic groups with this genetic susceptibility, decreasing the prevalence of diabetes relies almost exclusively on lifestyle modification.

Socioeconomic/Employment Status

Socioeconomic status has also been shown to correlate with the risk of developing diabetes. In regions with depressed economic development, the prevalence of T2DM is elevated in the upper classes; however, in regions with increased wealth, the rates of T2DM are increased 2–4 times in groups with low socioeconomic status and may be exacerbated by healthcare access and quality, that are dependent on payment [2, 14, 15]. In the United States, Everson et al. discussed an inverse relationship for diagnoses of T2DM when comparing a patient's education level, occupation, and income [13–15]. There also appeared to be a higher prevalence of diabetes with the poverty income ratio (i.e., annual income divided by federal poverty line) and low socioeconomic status. Evaluating education in this same study, Everson at al. also reported that the prevalence of diabetes was almost three times greater in adults with less than 9 years of education than adults with at least a high school diploma [16–18]. These social determinants (e.g., education, employment security, housing, access to nutritious food) also relate to the development and progression of diabetes through the pathways of psychological, physiological, and behavioral responses (e.g., chronic stress, development of mental health conditions). After diabetes diagnosis, health disparity and disease progression may persist due to financial burden, insufficient access to quality healthcare and other resources to manage the disease, as well as employment- and education-limiting effects [15]. These disparities are illustrated by the high rates of uncontrolled diabetes ($HbA_{1C} \geq 9$ %), 48.7 % and 27.3 %, in patients insured with Medicaid and Medicare, respectively [19, 20]. Additionally, socioeconomic status may overlap with genetically

vulnerable populations, and these groups may be confronted with the inability to overcome "obesogenic" environmental factors, resulting in increased rates of diabetes [2, 9].

Environment

Environmental causes have also played a role in developing and allowing DM to worsen. A spatial analysis study, integrating data from the CDC and United States Census Bureau, analyzed associations between diabetes prevalence and environmental factors including previously discussed primary factors such as race/ethnicity population percentages, education level, unemployment level, and poverty level. Also discussed were secondary factors including population density, percentages of obesity, physical inactivity, cycling/walking to work, and the consumption of food deserts. Excluding the aforementioned primary factors, the only significant finding in the secondary factors was a positive correlation between cycling/walking to work and diabetes prevalence [21]. In addition, a meta-analysis of long-term noise exposure demonstrated that populations exposed to day–evening–night noise levels, greater than 60 decibels (dB) in their primary residence, had a 16–22 % higher risk of developing Type 2 diabetes than populations exposed to less than 64 dB [17]. Increased risk was only found with exposure to increased noise in the residential environment, not occupational noise exposure. Additionally, animal-based studies of chronic noise exposure have described a decrease in plasma testosterone, which may be translatable to testosterone deficiency and increased risk of cardiovascular complications in men with diabetes [22–24].

Epidemiology

The National Diabetes Statistic Report (NDSR), an effort by the Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), American Diabetes Association (ADA), and other organizations, was released in 2014 [1]. The report indicated that 29.1 million people in the United States, or 9.3 % of the entire population, were currently living with diabetes, with 21.0 million as diagnosed and 8.1 million as undiagnosed. In 2012, the new diagnoses in the one-year period were 1.7 million [1]. Internationally, the International Diabetes Federation (IDF) has reported that 387 million people (8.3 %) were living with diabetes as of 2014, with almost 179 million people (46.3 %) classified as undiagnosed cases [5].

Association Between Diabetes, Chronic Conditions, and Surgical Outcomes

The major complications associated with DM include cardiovascular disease (CVD), nephropathy, retinopathy, neuropathy, and foot care, according to the ADA. By far, CVD is the most expensive complication in terms of direct and indirect costs. The ADA has estimated that the annual cost of CVD in the diabetic population is approximately $17.6 million, which includes office, emergency, and outpatient visits as well as inpatient, nursing home, home health, and hospice care [25]. In addition, T2DM often presents with hypertension and dyslipidemia, which leads to microvascular complications. Nearly 80 % of patients in the T2DM population will eventually be diagnosed with microvascular disease, and the diabetic population has a two times greater risk of myocardial infarction and stroke compared to the general population [26, 27]. Nephropathy is also identified and is the leading cause of end stage renal disease occurring in 20–40 % of the DM population. Chronic albuminuria is an early diagnostic marker of nephropathy in T1DM, of disease development in T2DM, and increased risk of CVD [28–31]. Additionally, the osteoinductive factor may also be a biomarker for early diagnosis of diabetic nephropathy in T2DM patients [32]. Another vascular-related complication of DM is retinopathy, which affects almost all T1DM patients and more than 60 % of T2DM patients within 20 years of disease onset [33].

Various neuropathic conditions are also prevalent, including distal symmetric polyneuropathy (DPN), diabetic autonomic neuropathy, cardiovascular autonomic neuropathy (CAN), gastrointestinal neuropathies, and genitourinary tract issues. All of these conditions may present as focal or multifocal and range in severity [34]. The DPN and autonomic neuropathies are the most common in DM, with DPN being asymptomatic in 50 % of patients. This increases the risk of foot-related injuries and complications.

Additional comorbid conditions include obstructive sleep apnea, fatty liver disease, cancer, decreased testosterone levels in men, periodontal disease, and hearing impairment [31]. Musculoskeletal conditions affecting the DM population include carpal tunnel syndrome, adhesive capsulitis (e.g., frozen shoulder), tenosynovitis, decreased joint mobility, hip fractures, and osteoporosis [35].

In addition, mental health conditions, are observed in greater numbers of patients with DM and include schizophrenia, bipolar disorder, anxiety disorders, and major depressive disorders [36, 37]. Studies have estimated that 12–27 % of the diabetic population experiences depression at a rate two to three times that of the general population [36–42]. Also, patients with mental health disorders have been shown to have an increased risk of developing diabetes [36], with Mezuk et al. describing a 60 % increased risk following a diagnosis of depression [43]. All of these mental health issues may be caused by stress, adversity (especially early in development), inflammation, hypothalamic–pituitary–adrenal axis dysregulation, psychiatric medications, along with sex- and comorbidity-based differences based on the development of mental health conditions in the DM population [41, 42, 44]. It is estimated that approximately 50 % of patients demonstrate decreased psychological health at the time of diabetes diagnosis. An international survey indicated that diabetes-related distress affected 13.8–44.6 % of people with diabetes [45].

Lastly, diabetic patients have often demonstrated inferior surgical outcomes and increased complication rates. Although the exact pathophysiology is unknown, it is postulated that hyperglycemia results in nonenzymatic protein glycation and formation of advanced glycation end products that modify enzymatic activity, immunogenicity, produce a decrease in protein half-life, and cause a decrease in ligand binding [46]. Ultimately, these factors increase the risk of wound and bone healing complications in hyperglycemic patients with or without diabetes [47]. A number of studies have tried to delineate specific risk factor parameters in diabetic patients undergoing surgical intervention, but no consensus has been achieved [47]. However, several factors have been suggested, including poor glycemic control, loss of protective sensation, chronic renal failure, and peripheral vascular disease. Even poor glycemic control, in the nondiabetic patient, has been shown to be associated with an increased risk of complications [47]. Acott et al. reported a perioperative complication rate of 26.4 % in the diabetic population, compared to 14.1 % in the nondiabetic population. Additionally, mortality has been shown to be increased in the diabetic population compared to the nondiabetic population (4.2 % vs. 1.0 %) [48].

Summary

In the United States, newly diagnosed cases of DM have increased overall since the CDC began publishing reports in 1980. However, since 2006 the number of new cases diagnosed per year has not significantly changed [49]. Internationally, trends in DM diagnoses vary. The IDF has published rates of diabetes prevalence by country and has defined rates of national prevalence ranging from 1.29 % (Mali; comparative rate = 1.6 %) to 37.37 % (Marshall Islands; comparative rate = 37.1 %) (comparative rate adjusted for age differences between countries/regions to allow comparison) [5]. Low- and middle-income countries are impacted with the highest rates of DM prevalence, as 77 % of all people with DM live in one of these countries.

Social science, basic science, and clinical studies have researched and continue to investigate rates of diabetes diagnoses, etiologies and

pathogeneses of diabetes as well as risk factors for diabetes. Published studies have identified five modifiable risk factors (obesity, physical activity level, diet, hypertriglyceridemia, and HDL cholesterol levels) related to incidence and methods to increase control of DM in the United states and the international population [50]. With a better understanding of DM, along with improved medical and surgical treatment options, the future care of diabetic patients will continue to decrease the morbidity and mortality associated with this patient population.

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