



Demographic and Clinical Factors Associated with Development of Type 2 Diabetes: A Review of the Literature

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Abstract: Diabetes mellitus is a complex and chronic condition that requires lifelong management and interaction with a healthcare system. Failure to control risk factors through preventive care may lead to a host of diabetes-related complications. Underperforming health care systems and poor awareness among the general population/healthcare professionals has been suggested as reasons why so many patients remain undiagnosed. Due to the asymptomatic nature of early and even intermediate diabetes mellitus, several years may pass without any diagnosis before complications begin to manifest. Other factors include age, gender, ethnicity, education, marital and unemployment status which may also increase the risk of developing morbidity and mortality associated with diabetes mellitus. This review summarizes the current demographic risk factors and clinical characteristics associated with diabetes mellitus. A literature search was conducted using PubMed, MEDLINE, and Sabinet by using the following search terms: diabetes mellitus, risk factors, characteristics and complications.

Keywords: diabetes mellitus, risk factors, characteristics, complications

Background

The number and prevalence of people with diabetes mellitus (DM) are rapidly rising. Diabetes is a chronic progressive condition that results in significant morbidity, premature death and economic burden to any healthcare system. Globally, as many as 5.0 million people aged between 20 and 99 years perished from diabetes-related mortality in 2017.¹ This makes DM more lethal than the combined number of deaths from HIV/AIDS (1.5 million), tuberculosis (1.5 million), and malaria (0.6 million), with almost half (46.6%) of the deaths aged <60 years.² According to the International Diabetes Federation (IDF), globally, there were 463 million people or 9.3% of the world's population living with diabetes in 2019, with 80% originating from low- and middle-income countries (LMICs).¹ Overall, it is estimated that 700 million or 10.9% of the world's population will have the disease by 2045 (Table 1).¹

Diabetes mellitus is a disorder characterised by glycaemic disturbances as a result of defects in insulin secretion, insulin action or both.³ Poor insulin action leads to abnormalities of carbohydrate, fat and protein metabolism in target tissues.⁴ Approximately 5–10% of patients with diabetes have type 1 diabetes mellitus (T1DM) which occurs through the destruction of pancreatic beta-cells.⁵ Patients

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Table 1 Estimated Total Number of Adults (20–79 Years) with Diabetes Mellitus in 2019, 2030 and 2045

	2019	2030	2045
Total Population			
Total world population	7.7 billion	8.6 billion	9.5 billion
Adult population (20–79 years)	5.0 billion	5.7 billion	6.4 billion
Diabetes Population (20–79 years)			
Global prevalence	9.3%	10.2%	10.9%
Number of people with diabetes	463.0 million	578.4 million	700.2 million
Number of deaths due to diabetes	4.2 million	–	–
Total health expenditures for diabetes*	USD 760.3 billion	USD 824.7 billion	USD 845.0 billion

Notes: *Health expenditures for people with diabetes are assumed to be on average two-fold higher than people without diabetes. Adapted with permission from International Diabetes Federation. *IDF Diabetes Atlas*. 9th ed. Brussels, Belgium: International Diabetes Federation; 2019. © 2019 International Diabetes Federation.¹

with T1DM are typically younger and absolutely insulin deficient, and therefore require exogenous insulin.⁶ Many patients with T1DM are highly susceptible to diabetic ketoacidosis (DKA), diabetic coma and/or even death.⁷ Aetiology has been postulated to be immune-mediated.⁸ Latent Autoimmune Diabetes in Adults (LADA) is, as the name suggests, T1DM which occurs later in life.⁸

The majority of patients with DM (90–95%) develop type 2 diabetes mellitus (T2DM).⁵ This type of DM arises through the gradual loss of insulin secretion which may be partly related to obesity, pancreatic beta-cell function decline and eventual hyperglycaemia.⁹ Patients with T2DM develop insulin resistance, which ranges from a relative deficiency to a complete insulin secretory defect.⁵ The aetiology of T2DM is most likely associated with the interaction between genes and the environment.¹⁰ A study by Pierce et al¹¹ demonstrated that a family history of T2DM increases the chances of developing this disease 2–4 fold. Similarly, there is a 40% lifetime risk of developing T2DM when at least one parent has the condition.¹² When both parents have T2DM the risk is increased to 70%. Environmental or epigenetic causes of T2DM are evident in the absence of concordance in monozygotic twins.¹³ The pathogenesis of DM may be influenced by dysbiosis of the intestinal microbiota whereby specific pathogens or metabolites produced by gut bacteria

have detrimental effects on metabolic pathways.¹⁴ Type 2 diabetes mellitus is considered a “disease of lifestyle”, hence frequently found in individuals with raised Body Mass Index (BMI), blood pressure and other cardiovascular risk factors. Therefore, management of T2DM includes changes in the diet and exercise routine, various forms of pharmacotherapy including combinations of antihyperglycaemic agents (oral and often insulin), antihypertensives, lipid-lowering and sometimes anti-platelet therapy.³

Diabetes

Globally, more than 600 million people are clinically obese.^{15,16} In the United States (US) alone, more than 1 in 3 adults and 17% of the youth were obese between 2011 and 2014.¹⁷ One study suggests that the obesity pandemic has gone as far as reaching two-thirds of adults living in the United States.¹⁸ Due to a worldwide increase in high-calorie diets, sedentary lifestyles and urbanization, obesity has now become an established risk factor for T2DM and/or metabolic syndrome (MS).¹⁹ Hence, the obesity prevalence is being paralleled by similar increases in the number of patients with T2DM or MS.²⁰ Often found in tandem in patients, raised BMI has been shown to be the strongest risk factor for the development of DM. Obesity is defined using cut points of BMI which measures the relationship between weight and height and is not age or gender dependent.²¹ On the other hand, total body fat varies by age, gender and ethnicity. Hu et al²² reported in an analyses of two cohorts that for every two extra years of a person being overweight there was a 9% increased risk of developing T2DM. In obese patients, the risk increased to 14% for patients exposed for the same duration. In addition to increased DM risk, obesity has been established as an independent risk factor for cardiovascular disease through its indirect influence on multiple comorbidities such as hyperlipidaemia, hypertension, insulin resistance, endothelial dysfunction and inflammation.²³ Certain minority ethnic groups seem to be at a higher risk of developing obesity and DM, whilst children/adolescents share equal risk as their adult counterparts.²⁴ In children it has been reported that as many as 41.3% spend more than 3 hrs a day engaged in video games or watching television, which was independently associated with weight gain.^{25,26} Rising trends in abdominal obesity in children and adolescents between 1988–1994 and 1999–2004 were as high as 65.4% (from 10.5% to 17.4%) for boys and 69.4% (from 10.5% to 17.8%) for girls.²⁷ In adolescents, T2DM arises from pathways that are similar to those proposed in

adults.²⁸ These range from insulin resistance to failure of pancreatic α -cells, β -cells, incretin production, kidney glucose filtration and lipolysis.²⁷ Likewise, complications and comorbidities develop in a similar fashion in adolescents as with adults with T2DM. However, adolescents with T2DM present with a disease that rapidly progresses, has treatment challenges, and both micro- and macrovascular complications develop at a rapid pace.²⁹ To treat hyperglycaemia in adolescents with T2DM, lifestyle modification together with biguanides (metformin) and/or insulin have been recommended.³⁰ For those who require additional long-term glycaemic improvements and weight loss, early bariatric surgery has a place, although not yet established as a mainstream option due to limited data.^{31,32}

Undiagnosed Diabetes Mellitus

As many as 175 million people are estimated to be undiagnosed and living with DM.³³ This figure ranges from as many as 24.1% to 75.1% of all diabetes cases across different regions, with 83.8% originating from LMICs.³² The Pacific Island populations have been shown to have the highest prevalence of undiagnosed DM.³² Underperforming healthcare systems and poor awareness among the general population/healthcare professionals have been suggested as reasons why so many patients remain undiagnosed. Other reasons include few or even an absence of symptoms which are commonly associated with the condition. The initial protracted and asymptomatic period of T2DM may last several years before a diagnosis of T2DM is finally made, which directly contributes to complications that arise.³ The following symptoms are characteristic of DM: thirst, polyuria, polydipsia, blurred vision, unexplained weight loss and polyphagia. The most devastating clinical manifestations are diabetic ketoacidosis (DKA) and a non-ketotic hyperosmolar state, both of which in the absence of treatment, result in lethargy, stupor, diabetic coma and/or death. According to Motala, DM was detected in 36% fewer patients (2.5% vs 3.9% of the cohort) when only the fasting plasma glucose test was performed rather than an oral glucose tolerance test (OGTT).³⁴ Hence, fewer patients with impaired glucose tolerance (pre-diabetes) would have been diagnosed. Plantinga et al³⁵ showed that in the US as many as 41.7% of individuals with previously undiagnosed DM presented with chronic renal disease. In China, diabetic retinopathy was found to be >30% among undiagnosed individuals with DM.³⁶ With undiagnosed DM carrying a similar risk of mortality as diagnosed DM, and

a 1.5- to 3.0-fold increased risk of mortality compared to non-diabetic individuals, there is clearly a major need for higher-quality screening.^{37,38}

Previous data have indicated that there are independent associations between age, age at diagnosis, diabetes duration and the risk of macrovascular events and/or death, whilst only diabetes duration is independently associated with the risk of microvascular complications.³⁹ Macrovascular complications may arise across all age groups (albeit more commonly in older DM patients). Hence younger patients with DM are more likely to develop microvascular complications earlier. One study proved that the development of retinopathy in patients with T1DM will occur after continuous exposure to hyperglycaemia.⁴⁰ However, the same study also showed the distinction between duration of exposure (at a certain threshold) and intensity of the hyperglycaemia, with the former risk factor having a greater effect on microvascular complications. Similarly, it has been demonstrated that retinopathy in patients with DM was more correlated with the duration of DM than with the age of onset of the disease.⁴¹ Therefore, earlier and more intensive control is needed in DM, particularly in overweight patients in order to minimize the risk of complications.

Complications Associated with Diabetes Mellitus

The T2DM condition is associated with a multitude of complications such as cardiovascular disease (CVD) and diabetic retinopathy, neuropathy and nephropathy.⁴² Rates of complications have been shown to be high in people with previously-undiagnosed DM compared to non-diabetic patients. As many as 25% of patients with T2DM present with retinopathy at diagnosis. Mbanya and Sobngwi⁴³ showed that diabetic retinopathy complications are seen in 15–55% of DM patients, with a large percentage of these patients having proliferative retinopathy and/or macular oedema. Whilst 32–57% of DM patients develop renal complications (microalbuminuria or macroalbuminuria) within 5–10 years of their diabetes duration, half of the patients on maintenance haemodialysis also have a positive diagnosis for DM.^{42,44,45} In an article on the cardiovascular complications of DM in sub-Saharan Africa, the authors discuss the increasing prevalence of major and emerging cardiovascular risk factors and their role in the growing burden of cardiovascular disease.⁴⁶ Diabetes in all its forms is one of the main

cardiovascular risk factors. Close to 15% of patients with stroke have diabetes, approximately 30% of patients treated in cardiovascular intensive care units have diabetes, and 2 of every 3 diabetic patients will die as a result of cardiovascular complications.⁴⁵ Overall, patients with T2DM have mortality rates approximately twice those without diabetes of equivalent age. Clinical trials targeting modifiable risk factors have shown efficacy and reduction in complications associated with DM, thus, many of the challenges associated with DM are modifiable and offer the potential for improvement.⁴¹

Ethnicity/Culture

Evidence suggests that lifestyle habits and health behaviours are directly linked to risk factors and prevalence of DM.⁴⁷ While classical risk factors such as raised blood pressure, dyslipidaemia, smoking and obesity contribute towards the development of DM, there are considerable disparities in the susceptibilities of certain ethnic groups. For example, in a group of 3193 men and 561 women aged 40–69 years studied in the United Kingdom (UK), in comparison with the Caucasians the Asian group not only had a higher prevalence of DM (19% vs 4%) but also higher blood pressures, higher fasting and post-glucose serum insulin concentrations, higher plasma triglyceride, and lower HDL cholesterol concentrations.⁴⁸ In the same study, mean waist-hip girth ratios and trunk skinfolds were higher in the Asian group.⁴⁷ Similarly, angiography studies have shown that in comparison with Caucasians, Asians in the UK were more likely to have triple vessel disease, several lesions on angiography and non-discrete lesions.⁴⁹ More worrying is the fact that Asians generally have smaller total coronary vessel diameters compared with Caucasians, which may increase technical difficulties and affect therapeutic coronary interventions.⁵⁰ Statistical data from the US suggest that African American adults are at least 50% more likely to have DM than their Caucasian counterparts.⁵¹ Whilst no clear reasons were provided, contributing factors such as modern lifestyle factors (which promote obesity), socio-economic and direct genetic propensity or gene-environmental interactions were all postulated.⁵⁰ In a large, prospective cohort analysis of more than two million adult members of a Kaiser Permanente Northern California integrated healthcare delivery system, in which all participants had uniform access to healthcare, the DM prevalence and incidence rates in the combined Asian and Pacific Islanders group were greater than

Caucasians, but lower than Latinos or African Americans.⁵² Strikingly, the Pacific Islanders group had more than three times the incidence of DM relative to Caucasians, and a 75% increased DM incidence compared with African Americans and Latinos.⁵¹ If the analysis were to consider minority Asian subgroups, then the previous study's conclusions may have differed, given the fact that the larger subgroups (Chinese and Filipinos) most likely influenced the Asian group's overall standing.⁵³ Consequently, treatment of diabetes should not only be multifactorial, but also tailored to the cultural backgrounds of the patient. Cooper-Patrick et al⁵⁴ have shown that when patients and physicians share a similar ethnic background, better outcomes are observed. Hence, differences across ethnic diversities require different strategies in understanding and improving the health outcomes among distinct and perhaps higher-risk ethnic groups.

The Aging Process

As many as 10.9 million US adults aged ≥ 65 years have been diagnosed with DM.⁵⁵ The incidence rates tend to increase with age until approximately 65 years, after which both the incidence and prevalence rates seem to remain stable.⁵⁴ Diabetes mellitus in older adults who are diagnosed after the age of 65 years is known as “incident DM”, which differs from long-standing DM where onset occurs in middle age or earlier.⁵⁶ The regular anatomical and physiological changes associated with the aging process are in fact hastened with DM, resulting in a reduction in life expectancy.^{57,58} In fact, it has been shown that adults aged 55 to 64 years who had DM experienced a life expectancy reduction of up to 8 years.^{59,60} The continued exposure to hyperglycemia induces oxidative stress, which further results in systematic endothelial dysfunction and vascular complications. Several molecular mechanisms have been proposed to explain the hyperglycemia-induced tissue damage found in patients with DM, one of which includes formation of advanced glycation end-products (AGEs) which are responsible for the pathogenesis of diabetic complications such as retinopathy, nephropathy, neuropathy and cardiomyopathy.⁶¹

Gender Differences

There is growing evidence that T2DM and its complications are related to gender differences. These differences occur as a result of hormonal variations, sociocultural behaviours, environmental changes (diet, lifestyle, stress, attitudes) and gene-environment interactions.⁶² For

instance, men are more likely to be diagnosed with T2DM at an earlier age and with a lower BMI, whilst obesity, a strong risk factor of T2DM, is more commonly found in women upon diagnosis.⁶³ Thus, females who attain a higher BMI tend to develop DM faster than men. Although women without DM generally have less risk of cardiovascular events than men, a change in glucose metabolism appears to reverse this phenomenon.⁶⁴ This may be due to the fact that females have increased capacity for adipocyte enlargement which could lead to fat deposition abnormalities.⁶⁵ Furthermore, endocrine changes caused by the onset of menopause in women, lowers oestrogen production, leading to changes such as an increase in proinflammatory abdominal adipose tissue. As a result, the oestrogen-derived cardioprotection normally active in women is lost over time, increasing the cardiovascular risk.⁶⁶ In a pooled analysis of 900 000 individuals across 64 cohorts and 28,000 coronary events, DM accounted for a three-fold increase in the risk of incident heart disease in women, whereas men had a two-fold increase in risk.⁶⁷ Therefore, one cannot ignore the pronounced effects of sex hormones which regulate the body's metabolism, vasculature, and inflammation.

Education

Education affects the ability to make lifestyle decisions and/or self-manage a disease such as diabetes.⁶⁸ Individuals with lower education levels have been shown to have higher rates of sedentary lifestyle, obesity, and alcohol consumption, all of which are recognized risk factors for the development or worsening of diabetes.⁶⁷ Similarly, populations with lower literacy levels have been linked to a lower likelihood of using general preventive measures, which may lead to higher morbidity and mortality rates.⁶⁹ Conversely, well-educated groups have been shown to be more capable of navigating or following complicated self-care regimens as used in the treatment of conditions such as HIV/AIDS and DM, thereby resulting in better health outcomes.⁷⁰ Other studies have also found that education is linked to faster adoption of new medical technologies.⁷¹ One such study showed that in patients with DM the level of general education was significantly associated with referral.⁷² The authors concluded that their better-educated patients with DM were better advocates for their own health, and more likely to be referred earlier in the course of their condition. Therefore, differences in education contribute to health disparities.

Marital Status

Data have shown that there are health-augmenting outcomes associated with positive personal relationships, especially with marriage.⁷³ In comparison with unmarried people, marriage offers a continued, long-lasting supportive environment which may promote physical and mental health.⁷⁴ Higher rates of cardiovascular disease and premature mortality have been shown in individuals who have never been married vs those who have had their marriage ended through either death or divorce.⁷⁵ One study found that after a 22-year follow-up, a significantly increased risk of T2DM was found among unmarried men.⁷⁶ Interestingly, in an analysis of 379 men and women aged ≥ 70 years, diabetes was found to be less prevalent among married vs unmarried, widowed or divorced individuals,⁷⁷ and Martin et al⁷⁸ found that there was a higher prevalence of DM among the widowed in comparison with married subjects. The theories which support the above include the "protective" aspect of marriage which is lost when the significant other has left or died, leading to loneliness, depression, risky health habits, poorer physical and cognitive function, poor self-rated health and increased risk of institutionalization.^{73,79,80}

Employment Status

The onset of T2DM usually occurs during the working life of individuals, with peak incidence in the fourth decade of life.⁸¹ Employment-related stressors such as shift work and work stress may trigger the development of T2DM through overactivation of the hypothalamic–pituitary–adrenal (HPA) axis and cortisol production.^{82–84} However, there is also evidence that individuals who lose their job are at greater risk of developing chronic diseases.⁸⁵ The rate of cardiovascular mortality is doubled in those who are unemployed in comparison with employed people, particularly in the first year of unemployment.^{86,87} Unemployment may elevate lifestyle risk factors such as low nutrient diets, lack of exercise, increased smoking and alcohol abuse.⁸⁸ Other inappropriate health behaviours could arise from changes in social relationships and psychological disorders which follow financial difficulties.⁸⁹

Economic Impact of Diabetes Mellitus

In terms of the economic impact of DM, in the US Hogan et al⁹⁰ documented that the medical expenditures associated with the disease in 2002 were estimated to be 132 billion US dollars. Ten

years later (2012), the estimated costs were almost double (\$245 billion), of which \$176 billion was attributed to direct medical costs and \$69 billion for lost productivity costs.⁹¹ Complications and comorbidities associated with DM are responsible for the highest costs of diabetes management. For instance, Li et al⁹² demonstrated that females with a duration of DM ≥ 15 years, positive smoking history and several micro- and macrovascular complications attracted up to 50% more costs than those without the complications. In the same study, the most costly complication was end-stage renal disease treated with dialysis or transplantation, which was also approximately three to five times the cost of treating early-stage renal complications (microalbuminuria).⁹¹ Zhuo and colleagues estimated that 48–64% of the lifetime medical costs were attributable to DM-related complications, with 57% spent on macrovascular disease (stroke and coronary heart disease).⁹³ In addition, men diagnosed with T2DM when aged ≥ 65 years spent approximately 64% of their costs on the treatment of diabetes-related complications, whilst those diagnosed between 25 and 44 years spent $\leq 50\%$.⁹² Diabetes is a cost burden to any economy, but in particular, LMICs which is where 80% of the world's DM population originate.¹ In well-resourced high-income countries the economic burden lies with governments, whereas in LMICs, individuals with DM and their families often bear the brunt of high costs associated with insulin and other essential treatments.¹ The impact of DM includes work disabilities, early retirement, loss of income/savings, lost work hours, absenteeism and presenteeism, most of which have negative effects on employment chances or work performance.⁹⁴ A study by Travis Minor found that the employment probability of patients with T2DM is negatively impacted across both genders, and in addition, T2DM males are estimated to earn less than their healthier non-diabetic counterparts.⁹⁵ Specifically, T2DM males have a “wage penalty” of about 52% after having lived with the disease for over 20 years.⁹⁴ There is substantial expenditure associated with DM, its related complications as well as loss of productivity at work. Thus, it is necessary to pay closer attention to the control of risk factors and the disease itself through diabetes prevention and management programs, as well as to further prevent or reduce costly complications associated with the DM.

Conclusion

With the worldwide increase in high-calorie diets, sedentary lifestyles and urbanization, the prevalence of DM is rapidly mushrooming out of control. Yet, many individuals remain undiagnosed. Obesity has become established as one of the strongest risk factors for the development of DM and there

appears to be a worrying trend that individuals with lower education levels and/or relative affluence are driving obesity rates rather than the reverse. There are multiple debilitating complications, some of which (eg retinopathy) are correlated with the duration, rather than the time of onset of DM. In addition to the classical risk factors, gender and ethnic differences make particular groups more susceptible to the onset of DM or DM-related complications. Education levels, urban-living, employment and marital status contribute towards diabetes-related outcomes. There is substantial expenditure associated with DM, particularly diabetes-related complications. Lastly, the high prevalence of DM and its complications call for a multi-faceted strategy before the prospect of even further rises becomes a reality. Such a strategy could include the creation of public health awareness campaigns, improving current screening services, increasing diabetes educational efforts for healthcare professionals (HCPs) and non-HCPs (eg social workers) whilst further implementing diabetes specific treatment programmes and follow-up services, especially in under-served areas within developing countries.

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