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Diabetes Mellitus: An overview of the types, prevalence, comorbidity, complication, genetics, economic implication, and treatment

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Abstract

One of the deadliest diseases in existence today is diabetes. Due to its effect on the lives of people, it has attracted more attention recently. The causes of the various forms of diabetes, including type 1 and type 2, are discussed in the manuscript along with how they affect people. Younger people are more likely to get type 1 diabetes than older people, who are more likely to develop type 2. The manuscript also discusses the two forms of diabetes treatment options and strategies; in addition to how the illness affects the sufferers' quality of life. For several factors that are explained, it has been shown that poor and moderate-income countries are those that are more prone to having diabetes. Additionally, the condition is more likely to affect some races than others. One of the causes is obesity. According to statistics, those who are socially and economically poor experience the effects of the disease more severely. The progression of the illness over time has been accompanied by an increase in the number of persons who develop diabetes and an increase in the number of untimely deaths of those with the disease.

INTRODUCTION

Numerous diseases affect those who have them and diabetes is one of those diseases that have significant financial consequences for those who have it and it can also be lethal. Type 1 diabetes and type 2 diabetes are the two types. The former is more prevalent among children, whereas the latter is more prevalent among adults. However, there are risk factors that have been identified in children that could lead to the development of type 2 diabetes and have a negative impact on their health. Diabetes is known to cause other severe complications in patients, resulting in even more misery and premature death. Individuals' chances of developing diabetes are also affected by their race and ethnicity. Perhaps this is related to the social and economic factors surrounding these races. People suffering from this disease, fortunately, have intervention methods as well as treatment options.

CONCLUSION

Diabetes is a lifelong condition characterized by abnormalities in insulin secretion or action, or sometimes both ^[1]. Insulin is a hormone released by the pancreas that works as the primary messenger for glucose from consumed meals to flow from the bloodstream into the body's cells to be switched for glucose ^[2]. Diabetes affects the entire system and causes issues in specific organs such as the eyes, nerves, and kidneys ^[3]. Diabetes affects 9% of the adult population globally, according to the World Health Organization ^[2, 4, 5]. It is a developing pandemic that may be traced back to the fast rise in obesity and inactivity ^[3]. ¹² Diabetes is classified into two types: type 1 (insulin-dependent) and type 2 (non-insulin-dependent) (adult-onset) ^[1]. Diabetes is a significant cause of early illness globally, primarily increasing the risk of heart disease ^[4]. Diabetes affects 80% of the population in poor and middle-income nations, and unlike in wealthy countries, those most affected are adults between the ages of 35 and 64 ^[4]. Furthermore, the most economically and socially marginalized persons have the most burden of living with the condition and are frequently the most financially impacted ^[4, 5]. Diabetes' consequences are assessed not only by the rise in prevalence presented every year per capita but also through the rising number of early deaths ^[4]. While most

infectious illness loads diminish as technology improves and life expectancy rises, the impacts of diabetes continue to increase [4]. This study reviewed diabetes mellitus with an overview of the types, prevalence, comorbidity, complication, genetics, economic implication, and treatment.

METHODOLOGY

For literature reviews, the electronic databases Pub Med, Google Scholar, and Med Line Plus were searched. The search was limited to peer-reviewed publications published between January 1994 and November 2022 for the compiled data. Publications that had keywords like "diabetes mellitus" were chosen. The articles were then included after being evaluated for topic scope and relevance (Figure 1).

DIFFERENT TYPES OF DIABETES

Diabetes is a category of metabolic illnesses in which insulin plays a central role. There are several pathogenic pathways at work in the etiology of this illness [1]. They vary from autoimmune death of pancreatic beta cells, resulting in chronic insulin insufficiency, to a disease inhibiting insulin action [1]. The cause of this condition is an aberrant carbohydrate, lipid, and protein metabolism caused by insufficient or even defective insulin activity [1]. The major cause of hyperglycemia is a deficiency in either secretion or action of insulin at one or more sites along the route [1].

5

TYPE 1 DIABETES

Type 1 diabetes is triggered by an autoimmune response in which the body targets insulin-producing cells [1]. The level of beta cell breakdown in this form of diabetes differs from patient to patient, being fast in some and exceedingly sluggish in others [1].

Keto-acidosis is the most common initial symptom of the illness in most people [1]. Others exhibit symptoms such as fasting hyperglycemia as well as keto-acidosis in the context of environmental variables [1]. Although some people may preserve adequate beta-cell activity to prevent keto-acidosis, many individuals eventually become insulin dependent and develop keto-acidosis [1]. As the condition advances, insulin production decreases, and C-peptide levels become low, and often undetectable [1]. A variety of reasons, including heredity, environmental factors, and idiopathic causes can cause autoimmune degradation of beta cells [1]. Some people with type 1 diabetes have an unclear origin. While only a small percentage of individuals with this disease fit this description, those who do are typical of African or Asian origin [1].

TYPE 2 DIABETES

Type 2 diabetes affects 90-95% of the diabetic population. This kind of diabetes is characterized by a complicated process in which the fundamental issue is a balance between insulin production by beta cells and insulin action, resulting in insulin resistance to insulin-stimulated glucose [3]. Impaired glucose tolerance is the illness' intermediate stage that determines the risk of heart disease [1]. Many individuals with this type of condition are larger and somewhat obese, indicating that obesity has induced some sort of insulin resistance [1]. Keto-acidosis happens spontaneously and gradually in this kind of diabetes, and it is frequently triggered by the same conditions that cause type 1 diabetes: stress and illness. Because of the absence of apparent symptoms, this kind of diabetes is commonly undiagnosed [3]. Most of the symptoms develop in a reasonably slow progression and are frequently not severe enough to be detected [1].

REGIONAL OVERVIEWS

The diversity of socioeconomic, and geographical parameters, prevalence, associated death, and health expenditure may all be used to assess the Global Perspective [1, 2, 5]. Most diabetics reside in less developed and economically depressed parts of the world [5]. Eighty percent of the population is from low- to middle-income nations [1, 2, 5]. Different forms of diabetes are prevalent across the world, yet each has a distinctive impact on different populations [5, 6]. Infectious diseases and poverty, such as human immunodeficiency virus (HIV) and malaria, are prevalent in Africa [5]. This has now changed, attributable to a shift in lifestyle in urban and rural regions, which leads to an increase in obesity. "Diabetes has taken precedence in this region" and others [5, 6]. Europe is grouped into fifty-six countries, with socioeconomic levels ranging from low to high [7]. Age is the most important risk factor for diabetics. Diabetes is expected to affect 56 million people in Europe, with adults accounting for 8.5 percent [7]. The top three nations in the Middle East and North Africa with the highest comparative frequency are Saudi Arabia, Kuwait, and Qatar [6, 7]. The rapid rise in economic growth, along with an aging population, has led to a substantial rise in the prevalence of type 2 diabetes [4]. Rapid urbanization, lower infant mortality, and increasing life expectancy are the primary drivers of the rise in type 2 diabetes prevalence [4]. At 9.6%, North America and the Caribbean have the second-highest comparative prevalence of adult diabetes [4]. If the main North American countries of the United States (US), Mexico, and Canada were included in the figure because of their large population, the Caribbean islands would still have the greatest occurrence [4, 7]. Diabetes affects 38.6 million individuals in this region, with the number anticipated to climb to over 50 million by 2035 [7]. The US had the most diabetics, at 24.4 million [4].

DIABETES IN CHILDREN AND ADOLESCENTS

Diabetes is one of the most common disorders affecting school-aged children [8]. In 2012, around 208,000 young persons under the age of 20 in the US developed diabetes [8]. Additionally, during the COVID-19 pandemic, children with newly diagnosed type I

diabetes mellitus (T1DM) had higher glucose and HbA1c readings, necessitating specific actions to increase clinician and public awareness [9]. T1DM had a global incidence rate of 19.73 per 100,000 children in 2019 and 32.39 per 100,000 in 2020 [9]. The number of pediatric cases of new-onset T1DM, diabetic ketoacidosis, and severe diabetic ketoacidosis increased by 9.5%, 25%, and 19.5%, respectively, during the first year of the COVID-19 pandemic compared to pre-pandemic levels [9].

A high proportion of children and adolescents with type 2 diabetes are also susceptible to insulin resistance and have a family history of type 2 diabetes [8, 10]. Certain racial and ethnic groups, including African Americans, American Indians, Hispanic/Latino Americans, and some Asian and Pacific Islander Americans, have higher rates of type 2 diabetes [10]. Some children and adolescents with type 2 diabetes may not exhibit any signs or symptoms at all [10]. Other individuals' symptoms may resemble those of type 1 diabetes [10]. A toddler or teenager may feel tired, thirsty, or sick and require frequent urination [10]. Weight loss, hazy vision, recurring infections, and delayed wound/sore healing are all possible symptoms [10]. Because symptoms vary so much, healthcare practitioners must identify and evaluate children and adolescents who are at high risk for the condition [10]. The key to controlling type 2 diabetes in children is a balanced diet and quantity management, as well as increased physical activity [10, 11]. Metformin should also be recommended when type 2 diabetes is diagnosed [11]. However, data indicates that 50% of young people with type 2 diabetes will be unable to keep their hemoglobin A1c (HbA1c) below 8% on metformin alone, with or without lifestyle changes [11]. If metformin alone is insufficient to normalize blood glucose levels, insulin may be required [11, 12]. At the time of diagnosis, blood pressure, lipid profile, microalbuminuria evaluation, and dilated eye examination are all suggested tests [12].

DIABETES IN ADULTS

In 2020, diabetes was the eighth leading cause of mortality in the US, affecting more than 100,000 people [13]. Nearly one-fourth of all US persons with diabetes go undiagnosed, according to ¹³ the Centers for Disease Control and Prevention (CDC) National Diabetes Statistics Report [14]. Table 1 showed that this is particularly evident in younger adults aged 18-44 years [14]. More than 1/3 of the population with diabetes in this age range are unaware of or did not report having diabetes [14].

Though the trend in the incidence of diabetes among adults has been decreasing significantly since 2008, Table 2 below shows that there were still 1.4 million new cases in 2019 [15]. It is also worth noting that incidence rates are significantly higher among those with a high school education or less [16]. This indicates that more effort should be placed on health education among those of lower scholastic achievements [15, 16].

¹ TREATMENT OF DIABETES AMONG PEOPLE AGED 18 YEARS OR OLDER WITH DIAGNOSED DIABETES, UNITED STATES, 2015-2016

Diabetes management begins with healthy eating habits and physical activity. Since this may be challenging, medications are available to augment the achievement of better treatment results [17]. A retrospective, ⁹ cross-sectional analysis of the 2003-2016 National Health and Nutrition Examination Survey (NHANES) data was completed to investigate trends in ⁴ the use of diabetes medications [17]. Included were 6,323 patients, representing 26.5 million patients, 18 years and older ⁴ who had been told that they had diabetes, had an HbA1c greater than 6.4%, or had a fasting plasma glucose greater than 125 mg/dL [17]. The percentage of patients ⁴ taking any medication increased from 58% in 2003-2004 to 67% in 2015-2016 [17]. The ⁴ use of metformin and insulin analogs increased following American Diabetes Association (ADA) recommendations in 2007 where metformin was and continues to be preferred as first-line therapy for type 2 diabetes [17]. Among patients on one therapeutic agent, ¹⁰ the use of metformin increased from 33% in 2003-2004 to 74% in 2015-2016 [17]. Risk factors for type 2 diabetes in adults include: prediabetes, being overweight, age 45 years or older, family history of diabetes,

decreased physical inactivity, and history of gestational diabetes [18]. Figure 2 below details the distribution of diabetes across races/ethnicity. Diabetes is most prevalent among American Indians and Alaska Natives (14.5%), followed by Blacks (12.1%), people of Hispanic origin (11.8%), Asians (9.5%), and Whites (7.4%) [19].

CO-MORBID CONDITIONS

The autoimmune diseases autoimmune thyroiditis (AIT), celiac disease (CD), Addison's disease (AD), and vitiligo are frequently linked to T1DM [19]. In comparison to 0.5% of the general population, CD prevalence in T1DM patients ranges from 1.5% to 10% [20]. It is important to note that people who develop both illnesses have an earlier onset age for T1DM than patients who just have T1DM [20]. Furthermore, 3.4% to 50% of people with T1DM also have AIT [20]. Anti-thyroid antibodies are developed in 11% to 16.9% of T1DM patients within the first year of diagnosis, with females being more frequently impacted [20]. Up to 2% of T1DM patients may have anti-adrenal auto-antibodies [20]. It is commonly known that autoimmune diseases like diabetes and vitiligo are related. About 6% of diabetic children have it [20]. Additionally, T1DM has been linked to non-autoimmune diseases such as eating disorders [20].

The most common conditions seen in type II diabetes mellitus (T2DM), according to previous research and American Diabetes Association guidelines, are hyperlipidemia, hypertension, obesity, depression, chronic obstructive pulmonary disease (COPD)/asthma, coronary artery disease (CAD), chronic kidney disease (CKD), arthritis, cancers, neuropathy, heart failure, fractures, peripheral arterial disease, and retinopathy [21]. According to a study by Lin *et al.*, persons over 65 are more likely than those under 65 to have multiple co-morbid conditions [21]. Additionally, they discovered that older persons were less likely to be obese and depressed but more likely to have hyperlipidemia, hypertension, CAD, CKD, arthritis, malignancy, and heart failure [21].

With this information in mind, customized management plans should be created for frequent comorbidity clusters.

COMPLICATIONS

Diabetes can cause long-term harm to the heart, blood vessels, eyes, kidneys, and nerves. Smoking cigarettes, being overweight or obese, doing little to no physical activity, having high blood pressure, and having hyperlipidemia are risk factors for diabetes complications [22]. According to a multi-national study, heart disease and stroke account for 50% of diabetes-related deaths [23]. In comparison to adults without diabetes, those over the age of 18 had 1.7 times higher risk of dying from cardiovascular disease [24]. In 2011, the CDC found that nearly one-third of diabetics aged 35 or older had a history of heart disease or stroke. According to reports, coronary heart disease (21.9%) affects more people than stroke (9.1%) [22].

Diabetes has major complications that may be fatal, such as hyperglycemic crises, which include diabetic ketoacidosis and hyperglycemic hyperosmolar condition [20]. Death rates have progressively decreased over time, but 17.3 per 100,000 people still pass away each year [24]. In 2011, 44% of all new cases of renal failure were caused by diabetes. In the same year, 228,924 people of all ages were living with diabetes-related chronic dialysis or a kidney transplant, while 49,677 people of all ages started therapy for kidney failure [24]. The little blood vessels in the retina are harmed by diabetic retinopathy, which causes blindness. Diabetes is responsible for 1% of blindness worldwide [23]. Furthermore, diabetes has undesirable side effects of amputations. Foot neuropathy raises the risk of developing foot ulcers, getting infected, and ultimately needing an amputation [23]. Around 73,000 non-traumatic lower limb amputations occurred in 2010 for adult diabetics. Overall, these patients comprise about 60% of all non-traumatic lower-limb amputations in adults over the age of 20 [24].

GENETIC ROLE IN DIABETES MELLITUS: TYPE 1 DIABETES MELLITUS

One of the factors associated with those at risk of T1DM is genetic variation. In families, there is an inherited propensity for T1DM to develop [25]. It has been shown that the immune system can distinguish between proteins produced by the body's own cells and those produced by foreign invaders with the aid of the human leukocyte antigen (HLA) complex [25]. An increased risk of T1DM exists with some HLA variations on chromosome 6 [25]. Hundreds of genes that are known to play a role in the immune system are found in this area. The genes frequently linked to T1DM have been identified to be part of the HLA class II genes. These genes include HLA-DQA1, HLA-DQB1, and HLA-DRB1 [25].

An estimated 40–50% of the heritable risk for T1DM is attributed to HLA class II genes [26]. Researchers discovered a significant link between T1DM and the haplotypes DQA1*0501-DQB1*0201 and DQA1*0301-DQB1*0302 in Caucasian populations [26]. A haplotype is a group of single nucleotide polymorphisms (SNPs) that are located on the same chromosome [26]. Further research revealed that different races have different high-risk haplotypes for T1DM, such as DRB1*07-DQA1*0301-DQB1*0201 for African Americans, DRB1*09-DQA1*0301-DQB1*0303 for Japanese people, and DRB1*04-DQA1*0401-DQB1*0302 for Chinese people [26]. Additionally, it was discovered that DRB1*15-DQA1*0602-DQB1*0102 were protective and linked to a lower incidence of T1DM in most populations [26]. Recent studies reveal that independent of HLA class II genes, other genes in the central, class I, and extended class I areas may also enhance the risk of T1DM [26].

People with high-risk DRB1-DQA1-DQB1 haplotypes are substantially more likely to develop T1DM than people without such a haplotype [25]. According to studies, there is an approximately 6% absolute risk for Caucasian people with two susceptibility haplotypes to develop T1DM by the time they are 35 years old. However, in

populations where T1DM is uncommon, this number is much lower (1% among Asians). Two other genes, insulin (INS) and cytotoxic T lymphocyte-associated 4 (CTLA-4), are also known to affect the risk of T1DM as seen in Table 3 below [27,28].

GENETIC ROLE IN DIABETES MELLITUS: TYPE 2 DIABETES MELLITUS

The metabolic illness T2DM is characterized by hyperglycemia and a lack of insulin in the blood. One of the many factors contributing to T2DM is a genetic anomaly [26]. In 2011, several studies found that around 36 genes are connected to an elevated risk of T2DM. Due to these hereditary variables, only 10% of T2DM cases are clinically present [26]. Table 4 below lists the genes that are susceptible to acquiring T2DM [29].

Due to its function in adipose tissue and lipid metabolism, the peroxisome proliferator-activated receptors γ (PPAR γ) gene is crucial for study [30]. The PPAR γ gene's (Pro) function lowers insulin sensitivity while simultaneously raising the risk of T2DM [30]. In most populations, this gene is regarded as being quite prevalent [30]. At least one copy of the Pro allele is carried by 98% of Europeans. As a result, it probably accounts for a sizable part (25%) of T2DM in the Caucasian population [30].

Humans and most other mammals contain the protein known as ATP binding cassette, subfamily C, member 8 (ABCC8) [31]. Sulfonylurea receptor 1 (SUR1) protein is made with the help of this gene [31]. This protein and the Kir6.2 sub-unit, which is encoded by KCNJ11, are components of the ATP-sensitive potassium channel, which is crucial for controlling the release of the hormone's insulin and glucagon from the beta cells of the pancreas [31]. Insulin secretion and potassium channel function can both be impacted by a gene abnormality [31]. In the end, T2DM is the result of this. Intriguingly, the distance between ABCC8 and KCNJ11 – which is only 4.5 KB – is close to that of the INS gene [31]. ABCC8 (Ala) and KCNJ11 (Lys) gene variants have been linked to T2DM [30].

A ubiquitously expressed intracellular calcium-dependent cysteine protease known as calpain 10, which is prevalent in humans, is encoded by the CAPN10 gene [32]. An intrinsic adenine (A) to glycine (G) mutation at position 43 of a haplotype that was previously associated with T2DM appears to be important in CAPN10 transcription [32]. According to physiological research, the differences in calpain 10 activities' effects on insulin secretion increase the risk of T2DM [32]. Studies from various ethnic groups suggest that Mexican American communities may be considerably more likely than Caucasian populations to have an increase in T2DM risks because of this locus [32].

COST OF DIABETES

Diabetes economic expenses in the US rose by 26% between 2012 and 2017, after accounting for inflation, because of rising diabetes prevalence and per-person costs [33]. The population aged 65 and older is most affected by the rise in diabetes prevalence and medical expenses, which adds to the rising financial burden on the Medicare program [33]. The estimated \$327 billion total ¹¹ cost of diabetes diagnosis in 2017 includes \$237 billion in direct medical expenses and \$90 billion in lost productivity [33]. Average annual medical costs for individuals with diabetes are \$16,750, of which diabetes-related expenses account for \$9,000 of that total [33]. Medical costs for those with diabetes are, on average, 2.3 ⁸ times more expensive than they would be for people without the disease [33]. The indirect costs of diabetes include increased absenteeism (\$3.3 billion) and decreased productivity at work (\$26.9 billion) for the employed population, as well as decreased productivity for those who are not in the labor force (\$2.3 billion) [33]. In addition, indirect costs include the inability to work owing to disease-related disability (\$37.5 billion) and lost output as a result of 277,000 premature deaths that can be directly linked to diabetes (\$19.9 billion) [33].

TREATMENT

The course of treatment for diabetes varies from patient to patient depending on test results, particularly the levels of blood glucose ^[34]. Blood glucose control is the main objective of every treatment plan to avoid problems ^[34]. The primary treatment focuses for T1DM are insulin therapy, medication taken orally, exercise, and a diabetic diet ^[34]. The primary goals of T2DM are first weight loss and dietary advice. In the severe event where the aforementioned techniques fail to regulate blood glucose levels, oral medication will be administered next ^[34].

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