

Review (Narrative)

Diabetes Mellitus

Epidemiology, Treatment, and Pathogenesis

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SUMMARY

Diabetes mellitus is a group of metabolic disorders that are characterized by hyperglycemia due inadequate insulin action. The prevalence and incidence of diabetes are on the rise all over the world. Studies carried out by WHO projects such as the DIAMOND project reveal that even if type 1 diabetes prevalence is on the rise, type 2 diabetes is the major driver of the diabetes epidemic. There are various risk factors that may predispose an individual to diabetes mellitus. These factors include age, gender, genetics, environment and lifestyle. Diabetes mellitus is classified broadly as type 1 and type 2 diabetes mellitus. Other forms of diabetes mellitus such as idiopathic type one diabetes mellitus, fulminant type 1 diabetes, latent autoimmune diabetes in adults and maturity onset diabetes of the young. Insulin treatment is the mainstay of therapy for type 1 diabetes mellitus. Oral hypoglycemic agents such as metformin and sulfonylureas are majorly utilized in type 2 diabetes mellitus. Type 1 diabetes is due to autoimmune reactions leading to the destruction of beta cells in the pancreas and is usually seen in children. Type two diabetes, on the other hand, is associated with poor lifestyle choices such physical inactivity and unhealthy diet. All these mechanisms lead to insufficient production of insulin or impaired insulin sensitivity resulting in hyperglycemia. ■

KEYWORDS Diabetes mellitus; Epidemiology; Endocrine; Pathogenesis; Etiology

Sci Insig. 2016; 2016:e00132. doi:10.15354/si.16.re132

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DIABETES mellitus is a group of metabolic diseases characterized by chronic hyperglycemia due to insufficient insulin action. The common feature of this group of diseases is inadequate insulin action which leads to abnormalities in the metabolic system, including lipid, carbohydrate and protein metabolism. Diabetes mellitus can be caused by several factors including environmental and genetic factors. The principal mechanism for the development of diabetes is a decrease in the number of functional beta cells in the pancreas that results in the failure to provide adequate insulin action on the body organs. Various therapeutic means can be used to ameliorate insufficient insulin action. The patients are usually asymptomatic when the metabolic abnormality is mild. However, in instances where there are high levels of blood glucose levels symptoms such as polydipsia, polyphagia, polyuria, and weight loss can be seen. In extreme cases of hyperglycemic state occurs which can lead to coma or fatalities (1). Because of its high prevalence rates, diabetes mellitus is a condition that is being studied all over the world.

EPIDEMIOLOGY

Diabetes has become a huge concern in the world due to the rising prevalence of diabetes in the elderly, and the emergence of type 2 diabetes in children. In the next twenty years, the number of people diagnosed with diabetes is set to double. This projection is attributed to the increase in some people who are obese. Diabetes causes, symptoms and history vary from one population to another (2). Diabetes status has changed over the past from being a disease of the elderly to one affecting the middle-aged and the youth. The rise in prevalence is seen all over the world. Despite the fact that type 1 prevalence is on the rise, the major driver of the diabetes epidemic is type two diabetes. The World Health Organization (WHO) reported that India had the highest prevalence of Diabetes with over thirty-two million people having Diabetes mellitus. According to the International Diabetes Federation in 2006, the prevalence of diabetes in India was projected to rise from 40.9 million to 60.9 million by 2025 (3). Findings from multinational projects of the WHO such as the DIAMOND project, EURODIAB project and SEARCH study indicate that there are wide variations in the incidence and prevalence of type one diabetes mellitus. The DIAMOND project reported that in 2000 the incidence of type one

diabetes Mellitus in children below the age of fourteen years in fifty countries worldwide was at 4.5 per cent of the world's population. The lowest incidence of type one diabetes mellitus was reported in China and South America while the highest incidence was reported in Sweden, Norway, UK, Canada, Portugal, Finland and New Zealand. In the SEARCH study, type 1 diabetes prevalence was at 2.28 per cent in youths under the age of twenty (3). At the international level, the incidence and prevalence of type one diabetes mellitus dramatically vary. It is important to note that there is a positive relationship between distance north of the equator and incidence of type one diabetes mellitus. Norway and Finland have reported an annual 3.3 percent increase in the incidences of diabetes mellitus (4). It is reported that prevalence of type two diabetes mellitus in the United States is on the rise. An examination of twelve years of data from the Continuous NHANES, which was from 1999 to 2010 revealed that type two diabetes mellitus accounted for 43 per cent of all the cases of diabetes (5). There is a high prevalence of diagnosed type 2 diabetes which may be due to heightened awareness and early screening. According to Demmer (5), there exist disparities in the prevalence of both diagnosed and undiagnosed type 2 diabetes by sex in which diabetes is more prevalent in males than in females.

Various risk factors exist for the development of type one diabetes mellitus. Age is one of them as it is seen that type one diabetes mellitus is the major type of diabetes in youths. Gender is also a factor in the incidence of type one diabetes mellitus. Maahs (3) reports that in high incidence populations more males are diagnosed with type one diabetes mellitus than females. The converse is true in low incidence populations where more females than males have type one diabetes mellitus. Ethnicity and race also cause variations in worldwide prevalence rates. There exists an "Asian Phenotype" which refers to unique biochemical and clinical abnormalities in Asians which includes greater abdominal adiposity and increased insulin resistance. The so-called Asian phenotype predisposes Asians to diabetes. This explains that genetics, that is, the family history may be a risk factor for developing diabetes mellitus. Bao et. al (6), carried out a study to evaluate the predictive performance of genetic risk models. From the results of this study, they concluded that genetic risk models performed poorly in predicting the risk for type two diabetes mellitus. This shows that although genetics is implicated in the development of type 2 diabetes, predicting a

person's disposition to diabetes is almost impossible using genetic risk models. Kapoor et al. (7) reported from their study that the prevalence of diabetes mellitus was high among tribal tribes who were characterized by risk factors such as hypertension, obesity, physical inactivity and nonvegetarian diet. Urbanization leads to a change in the lifestyle and behavior of people with the development of lifestyle-related risk factors resulting in the prevalence of diabetes mellitus. Findings from different studies indicate that majority of cases are related to lifestyle cases. The results support the fact healthy and achievable dietary and physical activity among the older patients (8).

Medication use has also been associated with type 1 diabetes mellitus: systemic hormonal preparations except insulin and sex hormones, blood and blood-forming organs and systemic anti-infectives. Anti-infectives were the most frequently consumed drug categories in patients with type 1 diabetes mellitus. Gynecological antiseptics and anti-infectives were significantly associated with type 1 diabetes mellitus (9).

CLASSIFICATION OF DIABETES MELLITUS

Classification of diabetes mellitus is derived from etiology and pathophysiological stages. Etiological classification uses the terms type one and types two. Type 1 diabetes is associated with hereditary factors such as HLA (Human Leukocyte Antigen) alleles with other environmental factors such as viral infections. It usually develops in younger people, but it can occur in any age group (1). Symptoms of type 1 diabetes are polyuria, polydipsia, sudden weight loss, slow healing wounds, polyphagia, extreme tiredness and sudden weight loss. Idiopathic type 1 diabetes is a rare form of type 1 diabetes that is less severe than the autoimmune type 1 diabetes. Most of the patients that suffer from Idiopathic type 1 diabetes are of Asian or African origin. This form of type 1 diabetes is characterized by varying degrees of insulin deficiency and ketoacidosis. Fulminant type 1 diabetes was described first in the year 2000. It has some features that are similar to the idiopathic type 1 diabetes in that it is non-immune mediated and also characterized by ketoacidosis. It has been described majorly in East Asia. Genetic and environmental factors have been implicated in the onset and progress of the disease. Fulminant type 1 diabetes has also been associated with pregnancy (10).

Type 2 diabetes mellitus is associated with multiple genetic factors that lead to a decrease in insulin secretion or an increase in the development of insulin resistance compounded by lifestyle habits such as lack of exercise, overeating, obesity and environmental factors. Decreased insulin secretion and a decline in insulin sensitivity are implicated in the onset of type 2 diabetes. Type 2 diabetes mellitus is also referred to as non-insulin dependent type 2 diabetes mellitus. Pancreatic beta cell function is retained to a certain degree, and thus, insulin injections are rarely needed for survival. Ketoacidosis can occur as a result of infections. Obesity or a history of obesity is common in type 2 diabetes (1). Type 2 diabetes has mild symptoms, and this delays its diagnosis even for years. Insulin resistance has many manifestations such as nephropathy, obesity, hypertension and dyslipidemia. However, some patients with many features of type 2 diabetes also have some type 1 characteristics including the presence of autoantibodies to islet cells or GAD65. These patients have a distinct type of diabetes mellitus called LADA (Latent Autoimmune Diabetes in Adults) (11). The classification of LADA is, however, controversial.

Gestational diabetes mellitus develops during pregnancy. There is controversy on whether gestational diabetes mellitus should be classified on its own or not. However, due to its unique features that are different from diabetes in the absence of pregnancy. This is major because pregnancy itself worsens metabolism of glucose, diagnosis and control (1). Diabetes in pregnancy is associated with adverse effects for both the mother and child. It may lead to a caesarean section instead of normal delivery, preterm birth and hypertension in pregnancy (12). Kharroubi & Darwish (10) names other types of diabetes such as monogenic diabetes and disease of the exocrine pancreas. Monogenic diabetes is due to genetic defects in single genes in the pancreatic beta cells. It is classified according to the age of onset as neonatal diabetes or MODY (Maturity Onset Diabetes of the Young). Neonatal diabetes occurs before the age of six months and MODY before the age of 25 years. Disease of the exocrine pancreas is due to damage of beta cells through diffused injuries. Diffused injuries could be due to infection, pancreatitis, trauma, pancreatic carcinoma and pancreatectomy. Cirrhosis may also contribute to diabetes and insulin resistance.

Prediabetes is whereby individuals do not meet the criteria of having a diagnosis but are at a high risk of developing type 2 diabetes shortly. Persons who are de-

fined to have prediabetes have impaired fasting plasma glucose levels of between 5.6 to 6.9 mmol/L and impaired glucose tolerance test with two-hour plasma glucose levels in the oral glucose tolerance test of 7.8 to 11.0 mmol/L. However, the defining prediabetes using the levels above is misleading. It is therefore recommended that Hemoglobin A1c (HbA1c) levels of 5.7 percent to 6.4 percent be used in diagnosing prediabetes. There is a strong association between prediabetes and obesity and metabolic syndromes. It is, however, good to note that not all individuals who are diagnosed with prediabetes get diabetes in future. Exercise, weight loss, and healthy eating reduce the risk of developing diabetes (10).

THERAPEUTIC UPDATE OF DIABETES MELLITUS

Intensive insulin therapy is the mainstay of treatment of type 1 diabetes. The recommended therapy for type 1 diabetes consists of the following components; (i) multiple dose insulin injections tid (three times a day) or tds (four times a day) of basal and prandial insulin; (ii) matching prandial insulin to carbohydrate intake, premeal blood glucose, and anticipated activity; and (iii) for many patients (especially if glycemia is a problem), use of insulin analogs. For type 2 diabetes metformin along with lifestyle interventions is recommended at the time of diagnosis. In a newly diagnosed type 2 diabetic patients who have markedly elevated blood glucose levels insulin therapy should be considered along with additional agents. If at maximum doses, non-insulin therapy does not give the desired outcome, a second oral agent or insulin is given (13).

Oral hypoglycemic agents used in the treatment of diabetes mellitus include metformin which acts primarily through sensitization of the liver, thus reducing hepatic glucose output and consequently improving insulin resistance. Metformin is recommended as a first-line drug due to its effectiveness and low risk of hypoglycemia. Metformin should be avoided in patients with renal impairment. Thiazolidinediones are PPAR (Peroxisome Proliferation Activated Receptor- γ) agonists. They improve peripheral insulin sensitivity by increasing adipose tissue lipogenesis and reducing fat content and hepatic glucose production. Their use is however limited in the elderly due to their potential side effects. Alpha-glucosidase inhibitors target postprandial hyper-

glycemia by reducing digestion and absorption. What they risk of hypoglycemia is low when compared to other antidiabetics. This makes them agents of interest in the treatment of diabetes in the elderly. Insulin secretagogues such as sulfonylureas and meglitinides are also valuable in the treatment of type 2 diabetes. These drugs can be utilized as first, second-line or adjunctive therapy with metformin for the treatment of type 2 diabetes. Another class of antidiabetic drugs is gliptins. They are DPP4-1 (Dipeptidyl peptidase-4 Inhibitors). They can be used together with metformin if sulfonylureas pose a great risk of hypoglycemia.

There are emerging drugs that are showing promise in the treatment of diabetes mellitus. Recent studies have shown that a family of enzymes known as sirtuins may significantly increase life in various organisms. SIRT1 may have antidiabetic effects (14). The use of metformin in pregnancy has been evaluated. Compared to insulin, metformin was not implicated in perinatal complications (12). At present there is no convincing evidence that using medication to prevent the development of diabetes after gestational diabetes mellitus provides better long-term effects than using medications once the diabetes develops. Most antidiabetics have not been approved for use in gestational diabetes. Only metformin has been 'considered' by the American Diabetes Association (ADA). The focus should be on lifestyle changes and frequent monitoring of HbA1c levels in the patients that have diabetes mellitus (15). A study on the prescribing patterns in diabetes mellitus between 2000 and 2013 has shown that there has metformin is the mostly prescribed oral antihyperglycemic. Despite their limitations, sulfonylureas are the second most prescribed agents (16).

Lifestyle change is very important in the management of type 2 diabetes mellitus. Physical activities such as walking have been shown to reduce the risk of type 2 diabetes mellitus. Studies on diabetes prevention have demonstrated that diet change is core in preventing type 2 diabetes mellitus development. People should embrace healthy eating so as to reduce risks associated with the development of diabetes. Since obesity is one of the most important risk factors for type 2 diabetes mellitus, people who are obese should lose weight so as to reduce their chances of getting diabetes mellitus (17).

PATHOGENESIS OF DIABETES MELLITUS

Two major mechanisms characterize the pathogenesis of diabetes; insulin resistance and impaired beta cell function. Impaired beta cell function is the main defect observed in lean older patients while the older obese patients have relatively normal secretion of insulin but there is insulin resistance. Aging leads to muscle wasting and loss of strength through hormonal, neuronal, nutritional, immunological and physical activity mechanisms. When a muscle is lost in the elderly, fat infiltrates, and this infiltration has been shown to worsen insulin sensitivity. Loss of lean mass in the elderly is considered to be a worsening factor in insulin sensitivity (14). Type 1 diabetes mellitus is an autoimmune disease that ends up destroying the pancreatic beta cells (4). The destruction of the pancreatic beta cells increases the need for exogenous insulin. There is a 'honeymoon' period where residual beta cell function is restored. As the residual beta cell function diminishes, marked by extremely high levels of c-peptide in serum, management of type 1 diabetes mellitus becomes very complex especially for children (3).

In children and adolescents, type 2 diabetes is a complex metabolic disorder. Glucose balance largely depends on the balance between secretion of insulin by the pancreas and insulin action. The transition from impaired normal to impaired glucose tolerance has a correlation with worsening insulin resistance. Puberty plays a significant role in the development of type 2 diabetes mellitus in children. During adolescence, there is an increase in resistance to the action of insulin which results in hyperinsulinemia. After puberty, normal and stimulated responses to insulin decline. The increase in growth hormone levels during adolescence has been implicated in the development of insulin resistance in puberty (18). Impaired insulin action in type two diabetes mellitus and failure of the pancreatic beta cells to secrete insulin are the major mechanisms for the development of the disease. Florez (19) reported that seventeen loci had been convincingly associated with type 2 diabetes mellitus. The polymorphisms associated with these loci have some modest effects on risk. Genetic variation, therefore, is an underlying factor in the susceptibility of individuals to type 2 diabetes.

Obesity has adverse effects on glucose metabolism. Children who are obese become hyperinsulinemic and have lowered insulin-stimulated glucose metabolism compared with the children who are not obese. Expansion of adipose tissue in obese individuals synthesizes and secretes signaling metabolites such as adiponectin, leptin, and tumor necrosis factor- α . These proteins and metabolites are known to interfere with the secretion and sensitivity of insulin. Some experiments have shown that these factors may lead to insulin resistance under clinical and experimental conditions (20).

Gestational diabetes is characterized by unique inflammatory pathways. During a normal pregnancy, the balance of T-helper cell activity is strongly shifted towards an anti-inflammatory profile with Th2 cytokines playing a protective role in the fetal-maternal relationship. Inflammatory or infective actions tend to shift this balance and may compromise normal development. In the second trimester, insulin resistance increases to levels that are seen in type 2 diabetes mellitus. The normal pregnancy-induced insulin resistance is worsened by complications such as gestational diabetes (21).

CONCLUSIONS

Diabetes is a global health concern with prevalence rates on the rise as the years pass. Type 2 diabetes mellitus is the common type of diabetes mellitus accounting for up to ninety percent of all cases of diabetes mellitus. Type 2 diabetes mellitus is usually as a result of poor lifestyle choices such as bad eating habits, physical inactivity and obesity. These risk factors predispose individuals to type two diabetes mellitus. Type 1 diabetes mellitus arises due to an autoimmune reaction and is mainly witnessed in children. Diabetes mellitus is, however, manageable using antidiabetics and lifestyle change. To reduce the incidence and prevalence of diabetes mellitus, people should monitor their blood glucose regularly, and engage in physical exercises and healthy eating habits. ■

ARTICLE INFORMATION

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Author Contributions: Dr. Brosa had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: de Orduña.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: N/A.

Obtained funding: N/A.

Administrative, technical, or material support: Brosa.

Study supervision: Brosa.

Conflict of Interest Disclosures: All authors declared no competing interests of this manuscript submitted for publication.

Acknowledgement: N/A.

Funding/Support: N/A.

Role of the Funder/Sponsor: N/A.

How to Cite This Paper: de Orduña JP, Brosa J. Diabetes mellitus: Epidemiology, treatment, and pathogenesis. *Sci Insigt.* 2016; 2016:e00132.

Digital Object Identifier (DOI):

<http://dx.doi.org/10.15354/si.16.re132>.

Article Submission Information: Received, February 21, 2016; Revised: March 19, 2016; Accepted: March 26, 2016.

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