Diabetes mellitus: The epidemic of the century

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Abstract: Review of the prevalence of diabetes mellitus in various geographic areas. The Western Pacific area has the most people with diabetes diagnosed and the countries with the highest prevalence of diabetes (37.5%), whereas the Middle East and North Africa region has the highest incidence of diabetes in adults (10.9%), various types of diabetes mellitus The growth, regulation, and function of pancreatic cells at various levels, as well as a wide variety of mutations and single nucleotide polymorphisms in genes that affect these processes, are covered. The most significant developments in diabetes molecular understanding with respect to the many forms of diabetes compared to the earlier Here’s a quick summary of this field's understanding. The process of diabetes development and its consequences is still not fully understood, despite the vast amounts of data that have been accumulated at the molecular and cellular levels. There is unquestionably a need for more thorough research in this area, which will ultimately have an impact on improving diagnoses, and therapy, and reducing the likelihood of the emergence of chronic issues. The diagnostic standards, etiology, and genetics of type 1, type 2, gestational diabetes, and other kinds of diabetes mellitus are contrasted. Numerous eminent researchers and research teams in the biomedical field have given the molecular genetics of diabetes a great deal of attention lately.

Keywords: Diabetes, Classification of diabetes, Type 1 diabetes, Type 2 diabetes, Gestational diabetes, Diagnosis, Etiology, Genetics

Core tip: The prevalence of diabetes mellitus is alarmingly on the rise. Except for gestational diabetes, early detection of diabetes and prediabetes is crucial using the standard hemoglobin A1c criteria. Diabetes screening is crucial to preventing delayed diagnosis, especially in developing nations. The interplay of genetic and environmental factors plays a role in the development of diabetes. We are still learning new things about the mechanism of diabetes development from biomedical research, which is reviewed here. Recent research may offer tools for targeting a variety of genes for risk assessment, treatment plans, and complication prediction.

DEFINITION OF DIABETES MELLITUS:
A series of metabolic illnesses known as diabetes mellitus is characterised by persistent hyperglycemia brought on by deficiencies in insulin secretion, insulin action, or both. The significance of insulin as an anabolic hormone leads to metabolic irregularities in carbohydrates, lipids, and proteins. These metabolic abnormalities are brought on by insufficient insulin levels to produce an adequate response and/or insulin resistance of target tissues, primarily skeletal muscles, adipose tissue, and to a lesser extent, the liver, at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes. The kind and length of diabetes affect the severity of symptoms. Some people with diabetes have no symptoms, especially those who have type 2 diabetes in its early stages. Others have severe hyperglycemia, especially in youngsters.

CLASSIFICATION OF DIABETES MELLITUS:
Although categorization of diabetes is crucial and affects treatment strategies, it is challenging to do so because many patients, particularly younger adults, do not easily fit into a single class[1, 4-6] and 10% of those initially classified may need to be reclassified[7]. The American Diabetes Association (ADA) suggested a traditional categorization of diabetes in 1997, which included type 1, type 2, other forms, and gestational diabetes mellitus (GDM). This classification is currently the most often used and was adopted by the ADA[1]. The accelerator theory was put up by Wilkin[8], who claims that “type 1 and type 2 diabetes are the same disorder of insulin resistance set against different genetic backgrounds”[9]. The pace determines the difference between the two types, with a faster tempo representing a genotype that is more vulnerable and has an earlier appearance.

TYPE 1 DIABETES MELLITUS
Autoimmune type 1 diabetes
This kind of diabetes affects 5%–10% of people with diabetes[23] and is brought on by the death of pancreatic beta cells[24,25]. In children and adolescents, type 1 diabetes makes up 80–90% of cases of diabetes[2,26]. The number of children (0–14 years old) diagnosed with type 1 diabetes worldwide in 2013 was 497100 (Table (Table 1)), and there were 78900 new cases every year, according to the International Diabetes Federation (IDF)[27]. Due to the high prevalence of type 1 diabetes among adolescents and adults over the age of 14, these numbers do not accurately reflect the overall number of type 1 diabetes patients. According to one estimate, 3 million Americans had type 1 diabetes in 2010[28,29]. The proportion of children in the US that are under
prevalence of type 1 diabetes worldwide is unknown, it was 1.93 per 1000 youth under the age of 20 in the United States in 2009 (ranging from 0.35 to 2.55), with a 2.6% to 2.7% relative annual increase[26,31]. The main causes of type 1 diabetes arehumoral (B cell) and T-cell mediated inflammatory responses (insulitis) that result in the autoimmune death of pancreatic cells[25]. Type 1 diabetes is characterized by the existence of autoantibodies against the pancreatic islet cells, even though it is unclear how these antibodies contribute to the disease's pathophysiology. These autoantibodies include islet cell autoantibodies as well as antibodies to insulin (IAA), glutamic acid decarboxylase (GAD, GAD65), protein tyrosine phosphatase (IA2 and IA2), and zinc transporter protein (ZnT8A)[32]. These pancreatic autoantibodies, which are signs of type 1 diabetes, could be seen in the serum of these patients months or years before the beginning of the condition[33]. Strong HLA connections and links to the DR and DQ genes are associated with autoimmune type 1 diabetes. Both predisposing and protecting HLA-DR/DQ alleles exist[1]. This autoimmune type 1 diabetes is more prevalent in children and adolescents and is characterized by the lack of insulin secretion.

Symptoms of type 1 diabetes include polydipsia, polyuria, enuresis, lack of energy, extreme fatigue, polyphagia, sudden weight loss, slow wound healing, recurrent infections, and blurred vision[27], as well as severe dehydration and diabetic ketoacidosis in kids and teenagers. Compared to adults, children experience more severe symptoms. In addition to having autoimmune type 1 diabetes, these people are also more likely to have Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anemia[1]. A honeymoon phase that lasts weeks to months, or in rare cases 2-3 years, can break type 1 diabetes patients' total reliance on insulin. Some kids' need for insulin therapy may become so minimal that they don't even need it.

**Idiopathic type 1 diabetes**

A rare form of type 1 diabetes of unknown origin (idiopathic), less severe than autoimmune type 1 diabetes, and is not due to autoimmunity has been reported. Most patients with this type are of African or Asian descent and suffer from varying degrees of insulin deficiency and episodic ketoacidosis[45].

**Fulminant type 1 diabetes**

In addition to sharing some characteristics with idiopathic type 1 diabetes in that it is not immune mediated, this separate variant of type 1 diabetes was originally identified in 2000[46,47]. Ketoacidosis occurs shortly after the initiation of hyperglycemia, and blood C-peptide levels, which are a sign of endogenous insulin release, are undetectable. It has primarily been studied in East Asian nations and accounts for 5000–7000 cases, or 20%, of acute-onset type 1 diabetes patients in Japan[48,49]. It is characterized by an incredibly quick and practically total beta-cell death with almost no residual insulin secretion. Viral infection in particular has been linked to the condition, along with genetic and environmental variables. Pancreatic beta cell degeneration could be brought on by an increased immunological response to a viral infection.

**TYPES OF DIABETES MELLITUS**

**Monogenic diabetes**

The genetic etiology of diabetes can be characterized to help with diagnosis, treatment, and counseling[79]. A single gene in pancreatic cells has a genetic abnormality that disrupts cell function or a decrease in the number of cells, resulting in monogenic diabetes. Monogenic diabetes is typically divided into two categories based on when it first manifests: neonatal diabetes before the age of six months, or maturity-onset diabetes of the young (MODY) before the age of 25. But some familial defects show up as MODY, adult-onset diabetes, or neonatal diabetes[2,9,80]. Others think that categorizing diabetes as MODY or neonatal diabetes is no longer useful and that monogenic diabetes is now utilized to relate particular genetic causes of the disease to their particular treatment implications[79]. Depends on beta cell differentiation Angiopoietin-like protein 8 (ANGPTL8) may serve as a potential “betatrophin” that stimulates beta cell proliferation, although research on mice missing the ANGPTL8 active gene or overexpressing the protein found that it did not affect beta cell proliferation[82]. A point mutation in the mitochondrial DNA linked to deafness causes mitochondrial diabetes, and maternal transmission of the mutant DNA can cause diabetes to be inherited from mothers[1,83]. In some of these situations, glucose intolerance is caused by mutations that produce mutant insulin or by a failure to convert proinsulin to insulin. Hyperinsulinemia, mild hyperglycemia, and severe diabetes have all been linked to genetic abnormalities in the insulin receptor or the insulin signal transduction pathway[1].

**Disease of the exocrine pancreas**

Diabetes can be brought on by pancreatic damage that results from widespread pancreatic injury. This harm may be the result of trauma, infection, pancreatectomy, pancreatitis, or pancreatic carcinoma[1]. Progressive loss of cells results from exocrine pancreas atrophy[84]. Diabetes may result from pancreatic fat accumulation or pancreatic steatosis due to decreased insulin secretion, but it may take a while before the damage to beta cells manifests[85]. Before diabetes develops and the pancreas' exocrine function declines in these patients, extensive pancreatic damage is typically necessary[86]. Diabetes and insulin resistance may be exacerbated by cirrhosis in cystic fibrosis[2].
Hormones and drugs
Patients with endocrine disorders that cause excessive hormone secretion, such as growth hormone, glucocorticoids, glucagon, and epinephrine in certain endocrinopathies like acromegaly, Cushing's syndrome, glucagonoma, and pheochromocytoma, have been found to have diabetes[1]. Growth hormone is used to treat children with stunted growth, and glucocorticoids are utilized as medications to inhibit the immune system and in chemotherapy.

Genetic syndromes
Patients with a variety of genetic disorders, including Down syndrome, Klinefelter syndrome, Turner syndrome, and Wolfram syndrome, have been found to have diabetes[1].

DIAGNOSTIC CRITERIA FOR DIABETES MELLIITUS
HbA1c and retinopathy, cut-off values for glucose and HbA1c are estimated. Diabetes mellitus is diagnosed by a fasting plasma glucose of less than 126 mg/dL (7.0 mmol/L), a 2-h OGTT plasma glucose of more than 200 mg/dL (11.1 mmol/L), an HbA1c of less than 6.5% (48 mmol/mol), or a random plasma glucose of more than 200 mg/dL (11.1 mmol/L) combined with symptoms of hyperglycemia. The International Expert Committee advocated using HbA1c to diagnose diabetes in 2009[100], and the American Diabetes Association, the Endocrine Society, the World Health Organisation, and numerous other experts and organizations have supported this recommendation. The benefits and drawbacks of the various HbA1c has several advantages over FPG for diagnosing diabetes, including greater convenience, preanalytical stability, lower CV (3.6%) compared to FPG (5.7%) and 2h OGTT (16.6%), stronger correlation with microvascular complications, especially retinopathy, and a marker for glycemic control and glycation of proteins, which is the direct link between the diagnosis of diabetes and its complications[104–109]. The HbA1c test should be repeated in asymptomatic patients within two weeks to confirm a single, seemingly diagnostic result. Numerous nations and diverse ethnic groups support the HbA1c cutoff value of 6.5% (48 mmol/mol), but ethnicity appears to have an impact on the cutoff values for diagnosing diabetes[111,112]. Cut-off values of 5.5% (37 mmol/mol) and 6.5% (48 mmol/mol) in the National Health and Nutrition Examination Survey (NHANES III), 6.2% (44 mmol/mol) in a Pima Indian study, 6.3% (45 mmol/mol in an Egyptian study, as reported by Davidson[105]; and three cut-off values for Chinese[112] have also been reported.

MOLECULAR GENETICS OF DIABETES COMPLICATIONS
Several gene mutations and polymorphisms have also been linked to the clinical consequences of diabetes, in addition to the genetic causes of the disease. The accumulated data on diabetic patients with a range of micro- and macrovascular problems support the existence of significant hereditary variables that play a role in the emergence of different complications[200]. The genes ACE and AKR1B1 in nephropathy, VEGF and AKR1B1 in retinopathy, and ADIPOQ and GLUL in cardiovascular disorders have all been identified to be linked to diabetes complications[200]. A single SNP in the smooth muscle actin (ACTA2) gene promoter region has been linked to the degree of coronary artery stenosis in type 2 diabetes patients, according to a study on Chinese patients[201]. Additionally, the susceptibility gene for alpha kinase 1 Aldose reductase, the vascular endothelial growth receptor, and the receptor for advanced glycation product genes have also been strongly linked to the risk of diabetic retinopathy (DR)[204]. Particular polymorphisms in these genes appear to increase the risk of DR development in diabetes patients. In vitreous samples taken from diabetes patients with complications in comparison to diabetes patients without the issue and control individuals, a significant differential proteome (involving 56 out of 252 proteins) is evident[205]. It's interesting to note that a significant number of them (30 proteins) are associated with the kallikrein-kinin, coagulation, and complement systems, including prothrombin, alpha-1-antitrypsin, complement C3, and antithrombin III, which are higher in diabetic individuals with retinopathy[205]. Furthermore, there are two single nucleotide polymorphisms: prevention and/or treatment of diabetes-related nephropathy. Recently, it was demonstrated that there is a clear link between the elevated risk of ESRD in American Indian patients and circulating levels of tumor necrosis factors 1 and 2[207]. Diabetes and healthy bone formation and health are related. Studies utilizing animal models found that there was a considerable drop in the insulin receptor (IR) in osteoprogenitor cells, leading to thin, fragile, and highly fracture-prone bones[208]. Similar results were seen in animal models using IR knockdown mutants specific to the bone, pointing to the critical function of IR in the healthy formation of bones[208]. In adipose tissues, mitochondrial dysfunction is linked to type 2 diabetes.

CONCLUSION
These findings suggest that B7-I inhibition might be a useful target for Diabetes mellitus is the pandemic of the century, and it will spread further if early-stage diagnostic procedures are not effective. This study focuses on the many forms of diabetes as well as the reliable diagnostic criteria and techniques that should be applied when diagnosing diabetes and prediabetes. It is clear that diabetes is a complex illness with many genes contributing to its onset. The accurate identification of the genetic causes of diabetes may offer a vital tool to enhance diagnoses, treatment (more towards patient-specific, individualized therapy), and more efficient genetic counseling. Additionally, our in-depth understanding of the relationship between medical genetics and the chronic complications of diabetes will give us an extra advantage to postpone or eliminate these complications, which put enormous pressure on the body.
References
11. Tuomilehto J. Worldwide increase in incidence of Type I diabetes--the analysis of the data on published incidence trends. Diabetologia.