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REVIEW

Diabetes mellitus: The epidemic of the century

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Abstract

The epidemic nature of diabetes mellitus in different regions is reviewed. The Middle East and North Africa region has the highest prevalence of diabetes in adults (10.9%) whereas, the Western Pacific region has the highest number of adults diagnosed with diabetes and has countries with the highest prevalence of diabetes (37.5%). Different classes of diabetes mellitus, type 1, type 2, gestational diabetes and other types of diabetes mellitus are compared in terms of diagnostic criteria, etiology and genetics. The molecular genetics of diabetes received extensive attention in recent years by many prominent investigators and research groups in the biomedical field. A large array of mutations and single nucleotide polymorphisms in genes that play a role in the various steps and pathways involved in glucose metabolism and the development, control and function of pancreatic cells at various levels are reviewed. The major advances in the molecular understanding of diabetes in relation to the different types of diabetes in comparison to the previous understanding in this field are briefly reviewed here. Despite the accumulation of extensive data at the molecular and cellular levels, the mechanism of diabetes development and complications are still not fully understood. Definitely, more extensive research is needed in this field that will eventually reflect on the ultimate objective to improve diagnoses, therapy and minimize the chance of chronic complications development.

Key words: Diabetes; Classification of diabetes; Type 1 diabetes; Type 2 diabetes; Gestational diabetes; Diagnosis; Etiology; Genetics

Core tip: Diabetes mellitus is rising to an alarming epidemic level. Early diagnosis of diabetes and prediabetes is essential using recommended hemoglobin A1c criteria for different types except for gestational diabetes. Screening for diabetes especially in underdeveloped countries is essential to reduce late diagnosis. Diabetes development involves the interaction between genetic and non-genetic factors. Biomedical research continues

to provide new insights in our understanding of the mechanism of diabetes development that is reviewed here. Recent studies may provide tools for the use of several genes as targets for risk assessment, therapeutic strategies and prediction of complications.

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DEFINITION OF DIABETES MELLITUS

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Metabolic abnormalities in carbohydrates, lipids, and proteins result from the importance of insulin as an anabolic hormone. Low levels of insulin to achieve adequate response and/or insulin resistance of target tissues, mainly skeletal muscles, adipose tissue, and to a lesser extent, liver, at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes are responsible for these metabolic abnormalities. The severity of symptoms is due to the type and duration of diabetes. Some of the diabetes patients are asymptomatic especially those with type 2 diabetes during the early years of the disease, others with marked hyperglycemia and especially in children with absolute insulin deficiency may suffer from polyuria, polydipsia, polyphagia, weight loss, and blurred vision. Uncontrolled diabetes may lead to stupor, coma and if not treated death, due to ketoacidosis or rare from nonketotic hyperosmolar syndrome[1-3].

CLASSIFICATION OF DIABETES MELLITUS

Although classification of diabetes is important and has implications for the treatment strategies, this is not an easy task and many patients do not easily fit into a single class especially younger adults[1,4-6] and 10% of those initially classified may require revision[7]. The classical classification of diabetes as proposed by the American Diabetes Association (ADA) in 1997 as type 1, type 2, other types, and gestational diabetes mellitus (GDM) is still the most accepted classification and adopted by ADA[1]. Wilkin[8] proposed the accelerator hypothesis that argues "type 1 and type 2 diabetes are the same disorder of insulin resistance set against different genetic backgrounds"[9]. The difference between the two types relies on the tempo, the faster tempo reflecting the more susceptible genotype and earlier presentation in which obesity, and therefore, insulin resistance, is the center of the hypothesis. Other predictors of type 1 diabetes include increased height growth velocity[10,11] and impaired glucose sensitivity of β cells[12]. The implications of increased free radicals, oxidative stress, and many metabolic stressors in the development, pathogenesis and complications of diabetes mellitus[13-18] are very strong and well documented despite the inconsistency of the clinical trials using antioxidants in the treatment regimens of diabetes[19-21]. The female hormone 17-β estradiol acting through the estrogen receptor-α (ER-α) is essential for the development and preservation of pancreatic β cell function since it was clearly demonstrated that induced oxidative stress leads to β-cell destruction in ER-α knockout mouse. The ER-α receptor activity protects pancreatic islets against glucolipotoxicity and therefore prevents β-cell dysfunction[22].

TYPE 1 DIABETES MELLITUS

Autoimmune type 1 diabetes

This type of diabetes constitutes 5%-10% of subjects diagnosed with diabetes[23] and is due to destruction of β cells of the pancreas[24,25]. Type 1 diabetes accounts for 80%-90% of diabetes in children and adolescents[2,26]. According to International Diabetes Federation (IDF), the number of youth (0-14 years) diagnosed with type 1 diabetes worldwide in 2013 was 497100 (Table 1) and the number of newly diagnosed cases per year was 78900[27]. These figures do not represent the total number of type 1 diabetes patients because of the high prevalence of type 1 diabetes in adolescence and adults above 14 years of age. One reported estimate of type 1 diabetes in the United States in 2010 was 3 million[28,29]. The number of youth in the United States younger than 20 years with type 1 diabetes was estimated to be 166984 in the year 2009[30]. The prevalence of type 1 diabetes in the world is not known but in the United States in youth younger than 20 years was 1.93 per 1000 in 2009 (0.35-2.55 in different ethnic groups) with 2.6%-2.7% relative annual increase[26,31]. Type 1 diabetes is mainly due to an autoimmune destruction of the pancreatic β cells through T-cell mediated inflammatory response (insulitis) as well as a humoral (B cell) response[25]. The presence of autoantibodies against the pancreatic islet cells is the hallmark of type 1 diabetes, even though the role of these antibodies in the pathogenesis of the disease is not clear. These autoantibodies include islet cell autoantibodies, and autoantibodies to insulin (IAA), glutamic acid decarboxylase (GAD, GAD65), protein tyrosine phosphatase (IA2 and IA2β) and zinc transporter protein (ZnT8A)[32]. These pancreatic autoantibodies are characteristics of type 1 diabetes and could be detected in the serum of these patients months or years before the onset of the disease[33]. Autoimmune type 1 diabetes has strong HLA associations, with linkage to *DR* and *DQ* genes. HLA-DR/DQ alleles can be either predisposing or protective[1]. This autoimmune type 1 diabetes is

Table 1 Number of subjects with type 1 diabetes in children (0-14 years), with diabetes in adults (20-79 years) and with hyperglycemia (type 2 or gestational diabetes) in pregnancy (20-49 years)

Region	Type 1 diabetes in children (0-14 yr)		Diabetes in adults (20-79 yr)				Hyperglycemia in pregnancy (20-49 yr)	
	2013		2013		2035		2013	
	Number in thousands	Newly diagnosed in thousands	Number in millions	Comparative prevalence	Number in millions	Comparative prevalence	Cases in live births in millions	Comparative prevalence
Africa	39.1	6.4	19.8	5.7%	41.5	6.0%	4.6	14.4%
Europe	129.4	20.0	56.3	6.8%	68.9	7.1%	1.7	12.6%
Middle East and North Africa	64.0	10.7	34.6	10.9%	67.9	11.3%	3.4	17.5%
North America and Caribbean	108.6	16.7	36.8	9.6%	50.4	9.9%	0.9	10.4%
South and Central America	45.6	7.3	24.1	8.2%	38.5	8.2%	0.9	11.4%
South East Asia	77.9	12.5	72.1	8.7%	123.0	9.4%	6.3	25.0%
Western Pacific	32.5	5.3	138.2	8.1%	201.8	8.4%	3.7	11.9%
World	497.1	78.9	381.8	8.3%	592.0	8.8%	21.4	14.8%

Data extracted from International Diabetes Federation Diabetes Atlas, 6th ed, 2013.

characterized by the absence of insulin secretion and is more dominant in children and adolescents.

In addition to the importance of genetic predisposition in type 1 diabetes, several environmental factors have been implicated in the etiology of the disease[9,33]. Viral factors include congenital rubella[34,35], viral infection with enterovirus, rotavirus, herpes virus, cytomegalovirus, endogenous retrovirus[36,37] and Ljungan virus. Other factors include low vitamin D levels[38], prenatal exposure to pollutants, improved hygiene and living conditions decreased childhood infections in countries with high socioeconomic status leading to increased autoimmune diseases (hygiene hypothesis), early infant nutrition such as using cow's milk formula instead of breast feeding[39] in addition to insulin resistance in early childhood due to obesity or increased height growth velocity. The role of environmental factors remains controversial[40]. Recent evidence supported the causative effect of viral infections in diabetes[41-43].

Type 1 diabetes often develops suddenly and can produce symptoms such as polydipsia, polyuria, enuresis, lack of energy, extreme tiredness, polyphagia, sudden weight loss, slow-healing wounds, recurrent infections and blurred vision[27] with severe dehydration and diabetic ketoacidosis in children and adolescents. The symptoms are more severe in children compared to adults. These autoimmune type 1 diabetes patients are also prone to other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anemia[1]. The complete dependence on insulin of type 1 diabetes patients may be interrupted by a honeymoon phase which lasts weeks to months or in some cases 2-3 years. In some children, the requirement for insulin therapy may drop to a point where insulin therapy could be withdrawn temporarily without detectable hyperglycemia[44].

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

This is a distinct form of type 1 diabetes, first described in the year 2000, and has some common features with idiopathic type 1 diabetes being non-immune mediated[46,47]. It is characterized by ketoacidosis soon after the onset of hyperglycemia, high glucose levels (≥ 288 mg/dL) with undetectable levels of serum C-peptide, an indicator of endogenous insulin secretion[48]. It has been described mainly in East Asian countries and accounted for approximately 20% of acute-onset type 1 diabetes patients in Japan (5000-7000 cases) with an extremely rapid and almost complete beta-cell destruction resulting in nearly no residual insulin secretion[48,49]. Both genetic and environmental factors, especially viral infection, have been implicated in the disease. Anti-viral immune response may trigger the destruction of pancreatic beta cells through the accelerated immune reaction with no detectable autoantibodies against pancreatic beta cells[48,50]. Association of fulminant type 1 diabetes with pregnancy has also been reported[51].

TYPE 2 DIABETES MELLITUS

The global prevalence of diabetes in adults (20-79 years old) according to a report published in 2013 by the IDF was 8.3% (382 million people), with 14 million more men than women (198 million men *vs* 184 million women), the majority between the ages 40 and 59 years and the number is expected to rise beyond 592 million by 2035 with a 10.1% global prevalence.

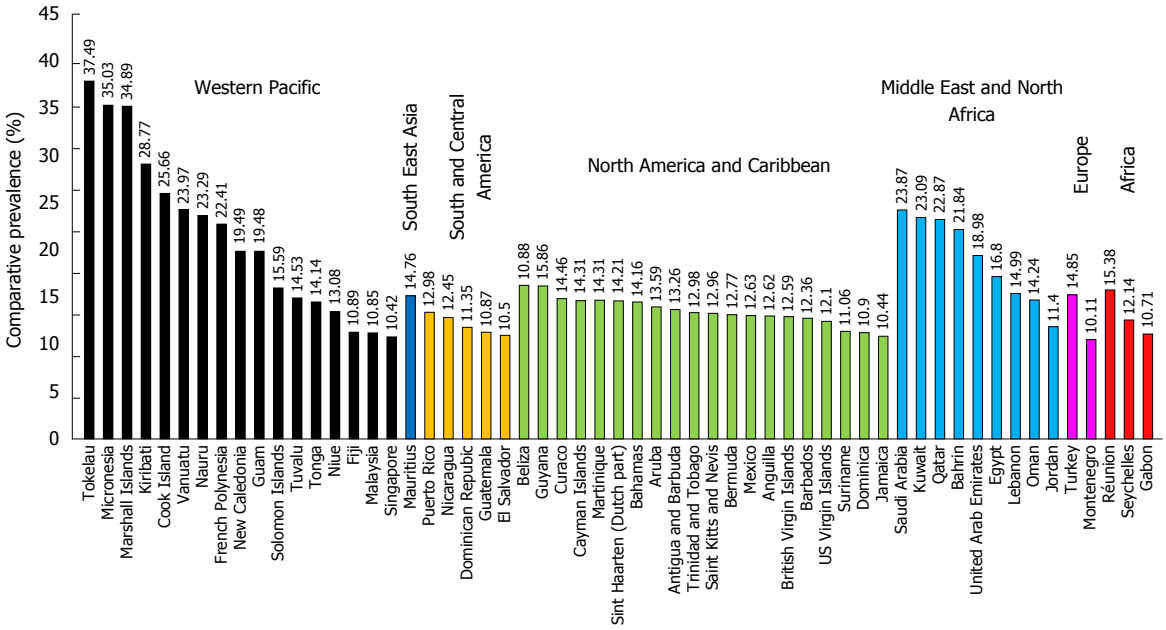

Figure 1 Comparative prevalence of diabetes in adults (20-79 years) in countries with high prevalence (≥ 10%). Data extracted from International Diabetes Federation Diabetes Atlas, 6th ed, 2013.

With 175 million cases still undiagnosed, the number of people currently suffering from diabetes exceeds half a billion. An additional 21 million women are diagnosed with hyperglycemia during pregnancy. The Middle East and North Africa region has the highest prevalence of diabetes (10.9%), however, Western Pacific region has the highest number of adults diagnosed with diabetes (138.2 millions) and has also countries with the highest prevalence (Figure 1)[27]. Low- and middle-income countries encompass 80% of the cases, "where the epidemic is gathering pace at alarming rates"[27]. Despite the fact that adult diabetes patients are mainly type 2 patients, it is not clear whether the reported 382 million adults diagnosed with diabetes also include type 1 diabetes patients.

More than 90%-95% of diabetes patients belong to this type and most of these patients are adults. The number of youth (less than 20 years) with type 2 diabetes in the United States in the year 2009 was 0.46 in 1000 and accounted for approximately 20% of type 2 diabetes in youth[26]. The increased incidence of type 2 diabetes in youth is mainly due to the change in the lifestyle of the children in terms of more sedentary life and less healthy food. Obesity is the major reason behind insulin resistance which is mainly responsible for type 2 diabetes[52-54]. The ADA recommends screening of overweight children and adolescence to detect type 2 diabetes[55,56]. The prevalence of obesity in children in on the rise[6] which is probably the main reason for the increased incidence of type 2 diabetes in the young (30.3% overall increase in type 2 diabetes in children and adolescence between 2001 and 2009)[26].

Insulin resistance in type 2 diabetes patients increases the demand for insulin in insulin-target tissues. In addition to insulin resistance, the increased demand for insulin could not be met by the pancreatic β cells due to defects in the function of these cells[18]. On the contrary, insulin secretion decreases with the increased demand for insulin by time due to the gradual destruction of β cells[57] that could transform some of type 2 diabetes patients from being independent to become dependent on insulin. Most type 2 diabetes patients are not dependent on insulin where insulin secretion continues and insulin depletion rarely occurs. Dependence on insulin is one of the major differences from type 1 diabetes. Other differences include the absence of ketoacidosis in most patients of type 2 diabetes and autoimmune destruction of β cells does not occur. Both type 1 and type 2 diabetes have genetic predisposition, however, it is stronger in type 2 but the genes are more characterized in type 1 (the *TCF7L2* gene is strongly associated with type 2 diabetes)[58]. Due to the mild symptoms of type 2 diabetes in the beginning, its diagnosis is usually delayed for years especially in countries where regular checkup without symptoms is not part of the culture. This delay in diagnosis could increase the incidence of long-term complications in type 2 diabetes patients since hyperglycemia is not treated during this undiagnosed period.

In addition to diabetes, insulin resistance has many manifestations that include obesity, nephropathy, essential hypertension, dyslipidemia (hypertriglyceridemia, low HDL, decreased LDL particle diameter, enhanced postprandial lipemia and remnant lipoprotein accumulation), ovarian hyperandrogenism and premature adrenarche, non-alcoholic fatty liver disease and systemic inflammation[6,54]. The presence of type 2 diabetes in children and adolescence who are

not obese[59-61], the occasional severe dehydration and the presence of ketoacidosis in some pediatric patients with type 2 diabetes[55] had led to the misclassification of type 2 to type 1 diabetes.

Some patients with many features of type 2 diabetes have some type 1 characteristics including the presence of islet cell autoantibodies or autoantibodies to GAD65 are classified as a distinct type of diabetes called latent autoimmune diabetes in adults (LADA)[62]. People diagnosed with LADA do not require insulin treatment. In a recent study, Hawa *et al*[63] reported 7.1% of European patients with type 2 diabetes with a mean age of 62 years, tested positive for GAD autoantibodies and the prevalence of LADA was higher in patients diagnosed with diabetes at a younger age. This classification of LADA as a distinct type of diabetes is still controversial[6,64-66].

Insulin resistance and signaling

Defects in the insulin-dependent substrate proteins IRS-1 and IRS-2 mediated signaling pathway are implicated in the development of metabolic disorders, mainly diabetes. This pathway mediates the cellular response to insulin and involves a large array of insulin-stimulated protein kinases including the serine/threonine kinase AKT and protein kinase C (PKC) that phosphorylate a large number of Ser/Thr residues in the insulin receptor substrate (IRS) proteins involved in the metabolic response to insulin[67]. In addition, other non-insulin dependent kinases including the AMP-activated protein kinase, c-Jun N-terminal protein kinase and G protein-coupled receptor kinase 2 that are activated under various conditions can phosphorylate the two insulin responsive substrates[67-71]. Disruption in the AKT and PKC kinases is central to the development of diabetes[72] and is associated with all major features of the disease including hyperinsulinemia, dyslipidemia and insulin resistance[73]. Replacing the wild type IRS-1 with a mutant version of the protein having alanine instead of tyrosine in three locations using genetic knock-in approach provided evidence to the central role of IRS-1 phosphorylation in the development of insulin resistance[74]. Using a similar approach to generate IRS-1 mutant with a single mutation involving a specific tyrosine residue, confirmed the role of IRS-1 phosphorylation in the development of insulin resistance pathogenesis[75]. The large cumulative evidence indicates a complex array of factors including environmental factors[76] and a wide range of cellular disturbances in glucose and lipid metabolism in various tissues[77] contribute to the development of insulin resistance. This condition generates complex cellular metabolic changes in a variety of tissues, mainly liver and muscles, that include the inability of the liver to transport and dispose glucose, control glucose production *via* gluconeogenesis, impaired storage of glucose as glycogen, *de novo* lipogenesis and hypertriglyceridemia[77]. Among the factors implicated in the development of insulin resistance, obesity is the most predominant risk factor leading to insulin insensitivity and diabetes which involves several mechanisms that participate in the pathogenesis of the disease[78]. Obesity-induced insulin resistance is directly linked to increased nutrient flux and energy accumulation in tissues that directly affect cell responsiveness to insulin[77]. However, it seems that other insulin-independent mechanisms are involved in the overall metabolic disturbances of glucose homeostasis and diabetes including activities in extra-hepatic tissues in addition to the central role of liver.

OTHER TYPES OF DIABETES MELLITUS

Monogenic diabetes

Characterization of the genetic etiology of diabetes enables more appropriate treatment, better prognosis, and counseling[79]. Monogenic diabetes is due to a genetic defect in single genes in pancreatic β cells which results in disruption of β cell function or a reduction in the number of β cells. Conventionally, monogenic diabetes is classified according to the age of onset as neonatal diabetes before the age of six months or Maturity Onset Diabetes of the Young (MODY) before the age of 25 years. However, certain familial defects are manifested in neonatal diabetes, MODY or adult onset diabetes[2,9,80]. Others believe that classification of diabetes as MODY and neonatal diabetes is obsolete and monogenic diabetes is currently used relating specific genetic etiologies with their specific treatment implications[79]. Beta cell differentiation depends on the expression of the homeodomain transcription factor PDX1 where mutation in the gene results in early onset diabetes (MODY) and its expression decreases before the onset of diabetes[81]. The angiopoietin-like protein 8 (ANGPTL8) may represent a potential "betatrophin" that acts to promote the proliferation of beta cells, however, studies using mice lacking the ANGPTL8 active gene or overexpressed protein indicated that it did not seem to play a role in beta cells proliferation[82].

Mitochondrial diabetes is due to a point mutation in the mitochondrial DNA associated with deafness and maternal transmission of the mutant DNA can result in maternally-inherited diabetes[1,83].

Mutations that result in mutant insulin or the inability to convert proinsulin to insulin result in glucose intolerance in some of these cases. Genetic defects in the insulin receptor or in the signal transduction pathway of insulin have been demonstrated to result in hyperinsulinemia and modest hyperglycemia to severe diabetes[1].

Disease of the exocrine pancreas

Damage of the β cells of the pancreas due to diffused injury of the pancreas can cause diabetes. This damage

could be due to pancreatic carcinoma, pancreatitis, infection, pancreatectomy, and trauma[1]. Atrophy of the exocrine pancreas leads to progressive loss of the β cells[84]. Accumulation of fat in the pancreas or pancreatic steatosis could lead to diabetes due to decreased insulin secretion but may require a long time before the damage to β cells occurs[85]. In most cases, extensive damage of the pancreas is required before diabetes occurs and the exocrine function of the pancreas is decreased in these patients[86]. Cirrhosis in cystic fibrosis may contribute to insulin resistance and diabetes[2].

Hormones and drugs

Diabetes has been found in patients with endocrine diseases that secrete excess hormones like growth hormone, glucocorticoids, glucagon and epinephrine in certain endocrinopathies like acromegaly, Cushing's syndrome, glucagonoma, and pheochromocytoma, respectively[1]. Some of these hormones are used as drugs such as glucocorticoids to suppress the immune system and in chemotherapy and growth hormone to treat children with stunted growth.

Genetic syndromes

Diabetes has been detected in patients with various genetic syndromes such as Down syndrome, Klinefelter syndrome, Turner syndrome and Wolfram syndrome[1].

PREDIABETES

Individuals with prediabetes do not meet the criteria of having diabetes but are at high risk to develop type 2 diabetes in the future. According to the ADA Expert Committee, individuals are defined to have prediabetes if they have either impaired fasting plasma glucose (IFG) levels between 100-125 mg/dL (5.6-6.9 mmol/L) or impaired glucose tolerance test (IGT) with 2-h plasma glucose levels in the oral glucose tolerance test (OGTT) of 140-199 mg/dL (7.8-11.0 mmol/L). The World Health Organization (WHO) still adopts the range for IFG from 110-125 mg/dL (6.1-6.9 mmol/L). Prediabetes has been shown to correlate with increased cardiovascular mortality[87,88] and cancer[89]. The definition of prediabetes with the indicated cut off values is misleading since lower levels of glucose in the normal range are still correlated with cardiovascular disease in a continuous glycemic risk perspective[90]. In accordance with the recommendation of the ADA in 2009 to use hemoglobin A1c (HbA1c) to diagnose diabetes, ADA also recommended the use of an HbA1c (5.7%-6.4%) to diagnose prediabetes[91]. The number of people with IGT according to IDF was 316 million in 2013 (global prevalence 6.9% in adults) and is expected to rise to 471 million in 2030[27]. According to a report in 2014 by the Center for Disease Control and Prevention, 86 million Americans (1 out of 3) have prediabetes[92]. Four of the top ten countries with the highest prevalence of prediabetes are in the Middle East Arab States of the Gulf (Kuwait, Qatar, UAE and Bahrin with prevalence of 17.9%, 17.1%, 16.6% and 16.3%, respectively)[27]. The number of people diagnosed with prediabetes is different according to the method and criteria used to diagnose prediabetes. The number of people with prediabetes defined by IFG 100-125 mg/dL is 4-5 folds higher than those diagnosed using the WHO criteria of 110-125 mg/dL[93]. Diabetes and prediabetes diagnosed using an HbA1c criteria give different estimates compared to methods using FPG or OGTT. Higher percentages of prediabetes were diagnosed using HbA1c compared to FPG[94-96]. Prediabetes is associated with metabolic syndrome and obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension[97]. Not all individuals with prediabetes develop diabetes in the future, exercise with a reduction of weight 5%-10% reduces the risk of developing diabetes considerably (40%-70%)[98]. Individuals with an HbA1c of 6.0%-6.5% have twice the risk of developing diabetes (25%-50%) in five years compared to those with an HbA1c of 5.5%-6.0%[99].

DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS

Diabetes mellitus is diagnosed using either the estimation of plasma glucose (FPG or OGTT) or HbA1c. Estimation of the cut off values for glucose and HbA1c is based on the association of FPG or HbA1c with retinopathy. Fasting plasma glucose of $\geqslant$ 126 mg/dL (7.0 mmol/L), plasma glucose after 2-h OGTT $\geqslant$ 200 mg/dL (11.1 mmol/L), HbA1c $\geqslant$ 6.5% (48 mmol/mol) or a random plasma glucose $\geqslant$ 200 mg/dL (11.1 mmol/L) along with symptoms of hyperglycemia is diagnostic of diabetes mellitus. In addition to monitor the treatment of diabetes, HbA1c has been recommended to diagnose diabetes by the International Expert Committee in 2009[100] and endorsed by ADA[101], the Endocrine Society, the WHO[102] and many scientists and related organizations all over the world. The advantages and disadvantages of the different tests used to diagnose diabetes have been reviewed by Sacks *et al*[103]. The advantages of using HbA1c over FPG to diagnose diabetes include greater convenience and 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 diagnosis of diabetes and its complications[104-109]. It is recommended to repeat the HbA1c test in asymptomatic patients within two weeks to reaffirm a single apparently diagnostic result[110].

A cut off value for HbA1c of $\geqslant$ 6.5% (48 mmol/mol) has been endorsed by many countries and dif-

ferent ethnic groups, yet ethnicity seems to affect the cut off values to diagnose diabetes[111,112]. Cut-off values of 5.5% (37 mmol/mol)[113] and 6.5% (48 mmol/mol)[114] have been reported in a Japanese study, 6.0% (42 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]. The Australians recommended the use of two cut-off values: ⩽ 5.5% to "rule-out" and ⩾ 7.0% to "rule-in" diabetes[115]. Variations in the prevalence of diabetes[94,116-119] and prediabetes[120] due to ethnicity have been documented. Most studies diagnosed less subjects with diabetes using HbA1c compared to FPG or OGTT[121-123]. Yet, other studies reported more subjects diagnosed with diabetes using HbA1c[96,124-126].

GESTATIONAL DIABETES

Hyperglycemia in pregnancy whether in the form of type 2 diabetes diagnosed before or during pregnancy or in the form gestational diabetes has an increased risk of adverse maternal, fetal and neonatal outcome. Mothers with gestational diabetes and babies born to such mothers have increased risk of developing diabetes later in life. Hyperglycemia in pregnancy is responsible for the increased risk for macrosomia (birth weight ⩾ 4.5 kg), large for gestational age births, preeclampsia, preterm birth and cesarean delivery due to large babies[127]. Risk factors for gestational diabetes include obesity, personal history of gestational diabetes, family history of diabetes, maternal age, polycystic ovary syndrome, sedentary life, and exposure to toxic factors[3].

Diagnosis of type 2 diabetes before or during pregnancy is based on criteria mentioned before. Fasting plasma glucose ⩾ 126 mg/dL (7.0 mmol/L) or 2-h plasma glucose ⩾ 200 mg/dL (11.1 mmol/L) after a 75 g oral glucose load. However, gestational diabetes has been diagnosed at 24-28 wk of gestation in women not previously diagnosed with diabetes using two approaches: the first approach is based on the "one-step" International Association of the Diabetes and Pregnancy Study Groups (IADPSG) consensus[128] and recently adopted by WHO[129]. Gestational diabetes is diagnosed using this method by FPG ⩾ 92 mg/dL (5.1 mmol/L), 1-h plasma glucose after a 75 g glucose load ⩾ 180 mg/dL (10.0 mmol/L) or 2-h plasma glucose after a 75 g glucose load ⩾ 153 mg/dL (8.5 mmol/L). This criteria is derived from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study[127] even though the HAPO study showed a continuous relationship between hyperglycemia and adverse short-term pregnancy outcome with no threshold reported[130]. The second approach is used in the United States and is based on the "two-step" NIH consensus[131]. In the first step 1-h plasma glucose after a 50 g glucose load under nonfasting state ⩾ 140 mg/dL (7.8 mmol/L) is followed by a second step under fasting conditions after a 100 g glucose load for those who screened abnormal in the first step. The diagnosis of gestational diabetes is made when at least two of the four plasma glucose levels are met. The four plasma glucose levels according to Carpenter/Coustan criteria are: FPG ⩾ 95 mg/dL (5.3 mmol/L); 1-h ⩾ 180 mg/dL (10.0 mmol/L); 2-h ⩾ 155 mg/dL (8.6 mmol/L); and 3-h ⩾ 140 mg/dL (7.8 mmol/L)[1].

The use IADPSC criteria in comparison with the Carpenter/Coustan criteria was associated with a 3.5-fold increase in GDM prevalence as well as significant improvements in pregnancy outcomes, and was cost-effective[132]. In another retrospective cohort study of women diagnosed with gestational diabetes, Ethridge *et al*[133] have shown that newborns of women diagnosed with gestational diabetes by IADPSG approach have greater measures of fetal overgrowth compared with Carpenter-Coustan "two-step" approach neonates. A strategy of using fasting plasma glucose as a screening test and to determine the need for OGTT is valid[134,135]. According to Sacks[136], correlation of glucose concentrations and the risk of subsequent complications will eventually lead to universal guidelines.

The use of ADA/WHO cut off value of HbA1c ⩾ 6.5% (48 mmol/mol) to diagnose gestational diabetes is not recommended by the "one step" IADPSC criteria or the "two-step" NIH criteria. Further investigation is required in light of recent reports on HbA1c in combination with OGTT and its usefulness to predict adverse effect of gestational diabetes or obviate the use OGTT in all women with gestational diabetes[137-141].

DIABETES AND GENETICS

Diabetes is a complex disease that involves a wide range of genetic and environmental factors. Over the past several years, many studies have focused on the elucidation of the wide spectrum of genes that played a role in the molecular mechanism of diabetes development[142-144]. However, despite the vast flow of genetic information including the identification of many gene mutations and a large array of single nucleotide polymorphisms (SNPs) in many genes involved in the metabolic pathways that affect blood glucose levels, the exact genetic mechanism of diabetes remains elusive[145,146]. Evidently, a major complication is the fact that a single gene mutation or polymorphism will not impose the same effect among different individuals within a population or different populations. This variation is directly or indirectly affected by the overall genetic background at the individual, family or population levels that are potentially further complicated by interaction with highly variable environmental modifier factors[147,148].

Molecular genetics and type 2 diabetes

One of the major focuses of biomedical research is to delineate the collective and broad genetic variants in the

human genome that are involved in the development of diabetes. This major effort will potentially provide the necessary information to understand the molecular genetics of the different forms of diabetes including type 1, type 2 and monogenic neonatal diabetes among individuals of all populations and ethnic groups. Despite the fact that linkage and association studies allowed the identification and characterization of many candidate genes that are associated with type 2 diabetes[144,149,150], however, not all of these genes showed consistent and reproducible association with the disease[151]. Genome wide association studies (GWAS) in various populations identified 70 loci associated with type 2 diabetes and revealed positive linkage of many mutations and SNPs that influence the expression and physiological impact of the related proteins and risk to develop type 2 diabetes. One study involved several thousand type 2 diabetes patients and control subjects from the United Kingdom allowed the identification of several diabetes putative loci positioned in and around the *CDKAL1*, *CDKN2A/B*, *HHEX/IDE* and *SLC30A8* genes in addition to the contribution of a large number of other genetic variants that are involved in the development of the disease[152]. Two similar studies from the Finns and Swedish populations and the United States resulted in the identification of similar single nucleotide variants[153] that are linked to the risk of acquiring type 2 diabetes[154,155]. The study in the United States population included in addition to type 2 diabetes, the association of the identified SNPs with the level of triglycerides in the tested subjects[155]. These SNPs are located near several candidate genes including *IGFBP2* and *CDKAL1* and other genes in addition to several other variants that are located near or in genes firmly associated with the risk of acquiring type 2 diabetes. Other GWAS analysis studies were performed in the Chinese, Malays, and Asian-Indian populations which are distinct from the European and United States populations in addition to meta-analysis of data from other populations in the region revealed relevant findings among patients with European ancestry[156]. The results of the combined analysis showed significant association of SNPs in the *CDKAL1*, *CDKN2A/B*, *HHEX*, *KCNQ1* and *SLC30A8* genes after adjustment with gender and body mass index. More recently, meta-analysis of GWAS data involving African American type 2 diabetes patients identified similar loci to the previous studies with the addition of two novel loci, HLA-B and INS-IGF[157]. These results provide strong evidence of common genetic determinants including common specific genes that are linked to diabetes. A small list of specific genetic markers seem strongly associated with the risk of developing type 2 diabetes including the *TCF7L2*[158] and *CAPN10*[159,160] genes which also play a significant role in the risk and pathogenesis of the disease[158,159]. The association of *TCF7L2* gene variants with type 2 diabetes and its mechanism of action received special attention by several investigators[161,162]. Over expression of the protein was shown to decrease the sensitivity of beta islet cells to secrete insulin[163,164] and was more precisely involved in the regulation of secretary granule fusion that constitute a late event in insulin secretion pathway[165]. The role of TCF7L2 in insulin secretion was partially clarified[166] that involves modifying the effect of incretins on insulin secretion by lowering the sensitivity of beta cells to incretins. Several other genes have been found to be significantly associated with the risk of developing type 2 diabetes including a specific SNP in a hematopoietically-expressed homeobox (*HHEX*) gene[167]. The islet zinc transporter protein (SLC30A8)[168] showed positive correlation with the risk of developing type 2 diabetes where variant mutations in this gene seem protective against the disease which provides a potential tool for therapy[169]. More recently, a low frequency variant of the HNF1A identified by whole exome sequencing was associated with the risk of developing type 2 diabetes among the Latino population and potentially may serve as a screening tool[170]. Genetic variants and specific combined polymorphisms in the interleukin and related genes including interlukin-6 (*IL-6*), tumor necrosis factor-α and *IL-10* genes were found to be associated with greater risk of developing type 2 diabetes[171], in addition to genetic variants in the genes for *IL12B*, *IL23R* and *IL23A* genes[172]. In a study involving the hormone sensitive lipase responsible for lipolysis in adipose tissues, a deletion null mutation, which resulted in the absence of the protein from adipocytes, was reported to be associated with diabetes[173]. Nine specific rare variants in the peroxisome proliferator-activated receptor gamma (*PPARG*) gene that resulted in loss of the function of the protein in adipocytes differentiation, were significantly associated with the risk of developing type 2 diabetes[174]. In addition, certain SNPs in the alpha 2A adrenergic receptor (*ADRA2A*) gene, involved in the sympathetic nervous system control of insulin secretion and lipolysis, were found to be associated with obesity and type 2 diabetes[175]. Link analysis between the melatonin MT2 receptor (*MTNR1B*) gene, a G-protein coupled receptor, identified 14 mutant variants from 40 known variants revealed by exome sequencing, to be positively linked with type 2 diabetes[176]. The authors suggested that mutations in the *MT2* gene could provide a tool with other related genes in modifying therapy for type 2 diabetes patients based on their specific genetic background to formulate personalized therapies which potentially may ensures the optimum response. Interestingly, mutations in the clock[177,178] and *Bmal1*[179] transcription factor genes which are involved in beta cells biological clock affecting growth, survival and synaptic vesicle assembly in these cells, resulted in reduced insulin secretion and diabetes. Evidently, prominent metabolic functions involve the production of specific reactive metabolites, leading to oxidative stress, which affect lipids, proteins and other biological compounds leading to serious damage in

various tissues and organs. Mutations and SNPs in the antioxidant genes, including superoxide dismutase, catalase and glutathione peroxidase, that decrease their activity are implicated in the risk and pathogenesis of type 2 diabetes[180]. The metabolic syndrome was shown to be associated with the development of type 2 diabetes in a population that is described as highly endogenous especially in individuals over 45 years of age[181]. Since consanguinity marriages is high in this population, screening for this syndrome among families could provide an informative marker on the risk of developing type 2 diabetes[181].

Molecular genetics of type 1 diabetes

Even though type 1 diabetes is basically described as an autoimmune disease that results in the destruction of pancreatic beta cells, however, single gene mutations and SNPs have been found to be associated with the susceptibility to this type of diabetes. Initially, two gene mutations were linked to the development of type 1 diabetes including the autoimmune regulator (*AIRE*) gene which affect the immune tolerance to self antigens leading to autoimmunity[182] and the *FOXP3* gene which results in defective regulatory T cells[183]. In addition, a mutation in the histone deacetylase *SIRTI* gene predominantly expressed in beta cells involved in the regulation of insulin secretion[184] and played a role in modulating the sensitivity of peripheral tissues to insulin[185] was detected in type 1 diabetes patients[186]. Recently, additional mutations and SNPs in the *CTLA-4 +49A/G* and HLA-DQB1 and *INS* gene VNTR alleles were found to be associated with type 1 diabetes, which have the advantage of differentiating between Latent autoimmune type 1 diabetes and type 2 diabetes[187]. The HLA-DQB1, in combination with HLA-DR alleles and a polymorphism in *PTPN22* gene seem to be associated with the age onset of late type 1 diabetes[188,189]. Two specific polymorphisms in the promoter region of a transmembrane protein (DC-SIGN) gene expressed in macrophages and played an important role of T- cell activation and inflammation were found to be protective against type 1 diabetes[190]. An innovative non-parametric SNP enrichment tool using summary GWAS DATA allowed the identification of association between several transcription factors and type 1 diabetes and are located in a type 1 diabetes susceptibility region[191]. Nine SNP variants in several genes associated with type 1 diabetes, not including the major histocompatibility gene region, were identified using extensive GWAS analysis[192]. Furthermore, several novel SNPs in a region in chromosome 16 located in the *CLEC16A* gene were shown to be associated with type 1 diabetes and seem to function through the reduced expression of DEX1 in B lymphoblastoid cells[193]. Since more than 40 regions in the human genome were identified to be associated with the susceptibility to type 1 diabetes[194-196], a weighted risk model was developed utilizing selected genes SNPs could be used for testing infants for these genetic markers that could provide insights in the susceptibility to type 1 diabetes development or safe prevention of the disease among young children[197].

Molecular genetics of monogenic diabetes

A large array of genes were identified to be involved in the development of monogenic diabetes[80] which represent about 2%-5% of diabetes patients. Monogenic diabetes results primarily from gene defects that lead to a decrease in beta cell number or function. Monogenic diabetes genes were identified using linkage studies or code for proteins that directly affected glucose homeostasis. The majority of genes responsible for monogenetic diabetes code for either transcription factors that participate in the control of nuclear gene expression or proteins that are located on the cell membrane, cytoplasm and endoplasmic reticulum, proteins involved in insulin synthesis and secretion, exocrine pancreatic proteins and autoimmune diabetes proteins[80]. The collective function of these proteins is their participation in glucose metabolism at different levels. Evidently, the hierarchy of a specific gene in the overall glucose metabolism pathway determines the onset of diabetes in the patient and whether it is neonataly expressed or have late onset expression (adulthood). Consequently, molecular defects in the structure and function of these genes lead to the disturbance of plasma glucose level, the primary pathological sign of diabetes. The molecular mechanism of permanent neonatal diabetes mellitus (PNDP) in addition to MODY explains the observed phenotype of monogenetic diabetes that involves loss of function of the expressed mutant protein. The first gene implicated in monogenic diabetes was the glucokinase (*GCK*) gene[198] which functions as a pancreatic sensor for blood glucose where more than 70 mutations in the gene were identified that affected its activity[199]. A recent study on *GCK* gene mutations causing neonatal and childhood diabetes showed that the majority of mutations resulted in the loss of the enzyme function primarily due to protein instability[148,150]. Two hepatocytes nuclear factor genes that code for the HNF4A and HNF1A transcription factors were closely associated with MODY1 and MODY2[148,149]. Definitely, a whole list of other genes involved in monogenic diabetes are either overlooked or included in the genetic determinants of type 1 and type 2 diabetes which will be identified and clarified through more careful future studies.

MOLECULAR GENETICS OF DIABETES COMPLICATIONS

In addition to the genetic determinants of diabetes, several gene mutations and polymorphisms have been associated with the clinical complications of diabetes. The cumulative data on diabetes patients with a

variety of micro- and macrovascular complications support the presence of strong genetic factors involved in the development of various complications[200]. A list of genes have been reported that are associated with diabetes complications including *ACE* and *AKR1B1* in nephropathy, *VEGF* and *AKRB1* in retinopathy and *ADIPOQ* and *GLUL* in cardiovascular diseases[200]. A study on Chinese patients revealed a single SNP in the promoter region of the smooth muscle actin (*ACTA2*) gene correlates with the degree of coronary artery stenosis in type 2 diabetes patients[201]. Furthermore, the alpha kinase 1 gene (*ALPK1*) identified as a susceptibility gene for chronic kidney disease by GWAS[202], was demonstrated in type 2 diabetes patients[203]. Three additional genes have been strongly correlated with this risk of diabetic retinopathy (DR) including the vascular endothelial growth receptor, aldose reductase and the receptor for advanced glycation products genes[204] where specific polymorphisms in these genes seem to increase the risk of DR development in diabetes patients[204]. A significant differential proteome (involving 56 out of 252 proteins) is evident that characterizes vitreous samples obtained from diabetes patients with the complication in comparison to diabetes patients without the complication and control individuals[205]. Interestingly, a large portion of these proteins (30 proteins) belong to the kallikrein-kinin, coagulation and complement systems including complement C3, complement factor 1, prothrombin, alpha-1-antitrypsin and antithrombin III that are elevated in diabetic patients with retinopathy[205]. In addition, 2 single nucleotides polymorphisms in the human related *B7-I* gene seem to mediate podocyte injury in diabetic nephropathy[206]. Furthermore, increased concentration of the ligand of B7-1 correlates with the progression of end-stage renal disease (ESRD) in diabetes patients[206]. These results indicate that B7-I inhibition may serve as a potential target for diabetes nephropathy prevention and/or treatment. Recently, it was shown that direct correlation is evident between circulating levels of tumor necrosis factors 1 and 2 and increased risk of ESRD in American Indian patients[207]. The link between diabetes and proper bone development and health is evident. Studies using animal models with major significant reduction in insulin receptor (IR) in osteoprogenitor cells resulted in thin and rod-like weak bones with high risk of fractures[208]. Similar findings were observed in animal models with bone-specific IR knockdown animals which points to the central role of IR in the proper development of bones[208]. Type 2 diabetes is also associated with mitochondrial dysfunction in adipose tissues. Using knockout animal models of specific mitochondrial genes led to significant reduction in key electron transport complexes expression and eventually adipocytes death[209]. These animals exhibited Insulin resistance in addition to other complications that can potentially lead to cardiovascular disease[209].

CONCLUSION

Diabetes mellitus is the epidemic of the century and without effective diagnostic methods at an early stage, diabetes will continue to rise. This review focuses on the types of diabetes and the effective diagnostic methods and criteria to be used for diagnosis of diabetes and prediabetes. Evidently, diabetes is a complex disease with a large pool of genes that are involved in its development. The precise identification of the genetic bases of diabetes potentially provides an essential tool to improve diagnoses, therapy (more towards individualized patient targeted therapy) and better effective genetic counseling. Furthermore, our advanced knowledge of the association between medical genetics and the chronic complications of diabetes, will provide an additional advantage to delay or eradicate these complications that impose an immense pressure on patient's quality of life and the significantly rising cost of health-care services.

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