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REVIEW ARTICLE

Pathophysiology of diabetes: An overview

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ABSTRACT

Diabetes mellitus is a chronic heterogeneous metabolic disorder with complex pathogenesis. It is characterized by elevated blood glucose levels or hyperglycemia, which results from abnormalities in either insulin secretion or insulin action or both. Hyperglycemia manifests in various forms with a varied presentation and results in carbohydrate, fat, and protein metabolic dysfunctions. Long-term hyperglycemia often leads to various microvascular and macrovascular diabetic complications, which are mainly responsible for diabetes-associated morbidity and mortality. Hyperglycemia serves as the primary biomarker for the diagnosis of diabetes as well. In this review, we would be focusing on the classification of diabetes and its pathophysiology including that of its various types.

Key words: Diabetes mellitus, endocrinopathies, gestational diabetes, maturity-onset diabetes of the young, neonatal diabetes

INTRODUCTION

Diabetes mellitus (DM), also known simply as diabetes is a complex metabolic disorder characterized by hyperglycemia, a physiologically abnormal condition represented by continued elevated blood glucose levels. Hyperglycemia results from anomalies in either insulin secretion or insulin action or both and manifests in a chronic and heterogeneous manner as carbohydrate, fat, and protein metabolic dysfunctions. Diabetes follows a progressive pattern with complex pathogenesis and varied presentation.[1,2]

Hyperglycemia and its associated carbohydrate, fat, and protein metabolic dysfunctions affect multiple organs of the body and disrupt their normal functioning. These disruptions progress gradually and arise mostly due to the adverse effects of hyperglycemia and its associated metabolic anomalies on the normal structure and functioning of micro- and macrovasculature, which lie at the core of organ structure, and function throughout the body. The structural and functional disruptions in organ system vasculature lead to micro- and macrovascular complications. Organ damage, dysfunction, and, ultimately, organ failure characterize these complications and affect body organs, which include, in particular, eyes, kidneys, heart, and nerves. Eye-related complications result in retinopathy with progression to blindness. Kidney-associated complications lead to nephropathy and potential renal failure. Heart-related complications include hypertension and coronary heart disease. Nerve-associated complications lead to neuropathy, which can be autonomic and/or peripheral. Cardiovascular, gastrointestinal, and genitourinary (including sexual) dysfunctions are characteristic manifestations of autonomic neuropathy, whereas foot infections including ulcers requiring amputations and Charcot joint (osteoarthropathy) are often associated with long-term peripheral neuropathy.[3-5] The cerebrovascular disease, peripheral arterial disease, and coronary heart

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disease, together termed as atherosclerotic cardiovascular disease, are of common occurrence in diabetes and constitute one of the major causes of diabetes-associated morbidity and mortality.[1,4,5]

Diabetes with its ever-increasing global prevalence has emerged as one of the most important and challenging health issues confronting the human population of the present world. The increase in the prevalence of diabetes in most regions across the globe has been parallel to the rapid economic development, leading to urbanization and adoption of modern lifestyle habits.[6] In the year 2019, the number of adult people aged 20–79 years with diabetes has been estimated to be about 463 million, which represents 9.3% of the total world adult population. By the year 2030, this number has been estimated to increase to 578 million, representing 10.2% of the total world adult population and further increase to 700 million by the year 2045, which represents 10.9% of the total world adult population. In the year 2019, the prevalence of diabetes among men and women has been estimated to be 9.6% and 9.0%, respectively, of the total respective gender world population.[7] Furthermore, in the year 2019, approximately 4.2 million adult people aged 20–99 years died due to diabetes, and its associated complications and health expenditure on diabetes estimated to at least 760 billion USD, which represents 10% of the total spending on adults. Diabetes during pregnancy has been estimated to have affected more than 20 million live births (1 in 6 live births) in the year 2019.[8]

CLASSIFICATION AND PATHOPHYSIOLOGY

DM is characterized by complex pathogenesis and varied presentation and any classification of this disorder, therefore, is arbitrary, but nevertheless useful, and is often influenced by the physiological conditions present at the time of assessment and diagnosis. The classification currently used is based on both the etiology and the pathogenesis of disease and is useful in the clinical assessment of disease and for deciding the required therapy. According to this classification, diabetes can be divided into four main types or categories: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and diabetes caused or associated with certain specific conditions, pathologies, and/or disorders [Figure 1].[1,9]

Type 1 diabetes mellitus

T1DM, also known as type 1A DM or as per the previous nomenclature as insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes, constitutes about 5–10% of all the cases of diabetes. It is an autoimmune disorder characterized by T-cell-mediated destruction of pancreatic β-cells, which results in insulin deficiency and ultimately hyperglycemia.[10,11] The pathogenesis of this autoimmunity,

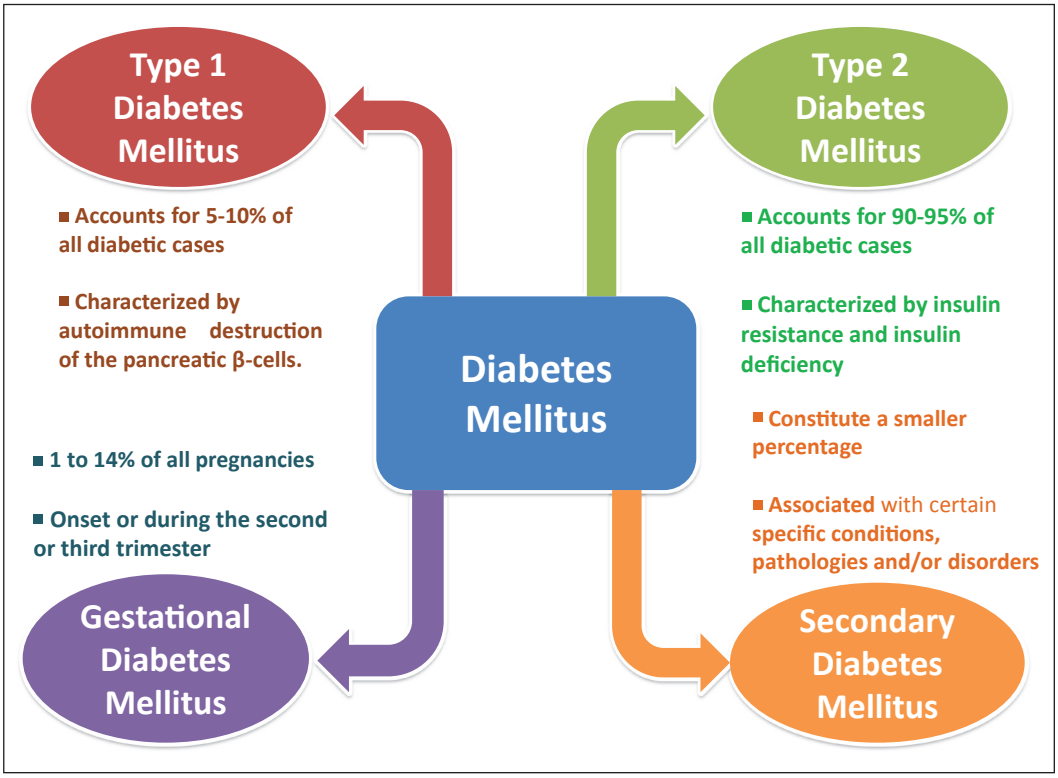

Figure 1: Four types of diabetes mellitus

though not yet fully understood, has been found to be influenced by both genetic and environmental factors. The rate of development of this pancreatic β-cell-specific autoimmunity and the disorder itself is rapid in most of the cases as in infants and children (juvenile onset) or may be gradual as in adults (late onset).

The variability in the rate at which the immune-mediated destruction of the pancreatic β-cells occurs often defines the eventual progression of this disease. In some cases, children and adolescents, the β-cell destruction and subsequent failure occur suddenly, which can lead to diabetic ketoacidosis (DKA), often described as the first manifestation of the disease. In others, the disease progression is very slow with a mild increase in fasting blood glucose levels, which assumes a severe hyperglycemic form with or without ketoacidosis, only in the presence of physiological stress conditions such as severe infections or onset of other disorders. In some other cases, which include adults, β-cells may retain some degree of function to secrete only that quantity of insulin, which is only sufficient to prevent ketoacidosis for many years. However, due to progressive insulin deficiency, these individuals become insulin-dependent with the emergence of severe hyperglycemia and subsequent ketoacidosis. Despite the variable progression of this type of diabetes, the affected individuals in the beginning or in the middle or even in the later stages of their life become severely or absolutely insulin-deficient and become dependent on insulin treatment for their survival. This severe or absolute insulin deficiency irrespective of its occurrence at any age manifests itself as low or undetectable levels of plasma C-peptide.[1,10,11]

T1DM is an autoimmune disorder characterized by several immune markers, in particular autoantibodies. These autoantibodies are associated with the immune-mediated β-cell destruction, characteristic of this disease. The autoantibodies include glutamic acid decarboxylase autoantibodies (GADAs) such as GAD65, islet cell autoantibodies (ICAs) to β-cell cytoplasmic proteins such as autoantibodies to islet cell antigen 512 (ICA512), autoantibodies to the tyrosine phosphatases, IA-2 and IA-2α, insulin autoantibodies (IAAs), and autoantibodies to islet-specific zinc transporter isoform 8 (ZnT8). At least one of these autoantibodies can be used for the clinical diagnosis of this disease but usually more of these immune markers have been observed in approximately 85–90% of patients with new-onset T1DM.[1,12] Of these autoantibodies, GAD65 is the most important and is present in about 80% of all T1DM individuals at the time of diagnosis, followed by ICAs present in 69–90% and IA-2α found in 54–75% of all T1DM individuals at clinical presentation.

The IAAs are important immune markers present in infants and young children who are prone to diabetes and its prevalence decreases as the age of onset of diabetes increases. The presence of IAAs in these individuals who have not been previously treated with insulin is an important indication of developing T1DM. IAAs are present in about 70% of all infants and young children at the time of diagnosis. The IAAs also play an important inhibitory role toward insulin function in patients on insulin therapy. Although not often clinically significant but nevertheless, this immune response has been observed with varying degrees of severity in at least 40% of patients on insulin treatment and therefore shows differential clinical manifestations.[13] These autoantibodies mostly consist of polyclonal immunoglobulin G (IgG) antibodies and differ in their affinities and binding capacities toward insulin. IAAs can either be high insulin affinity/low insulin-binding capacity or low insulin affinity/high insulin-binding capacity. The low insulin affinity/high insulin-binding capacity IAAs are responsible for clinical manifestations. At high titers, the binding of these antibodies to insulin prevents or delays its action and is responsible for characteristic hyperglycemia in the immediate postprandial period, which leads to significantly increased insulin requirements followed by unpredictable hypoglycemic episodes (postprandial hypoglycemia) observed later.[14]

These autoantibodies assume more clinical and diagnostic importance in some cases, particularly adults, with late-onset of this disease where the destruction of the pancreatic β-cells occurs at a very slow rate and often the disease masquerades as in T2DM. In such cases, these autoantibodies enable the correct diagnosis of this disorder as the T1DM, rather than the most common T2DM. This type of diabetes is often described as "Latent Autoimmune Diabetes in Adults (LADA)," also known as "slowly progressing insulin-dependent diabetes."[15]

LADA is the most common form of adult-onset autoimmune diabetes and accounts for 2–12% of all diabetic cases in the adult population.[16] Of the autoantibodies, GADAs are the most important and sensitive markers for LADA followed by ICAs. However, the IAAs, autoantibodies to the tyrosine phosphatases—IA-2 and IA-2α, and autoantibodies to islet-specific zinc transporter isoform 8 (ZnT8) which are observed in patients with juvenile- or young-onset T1DM are detectable in only a small number of cases in LADA.[17] In a study on LADA (Action LADA study), GADAs were the only diabetes-specific autoantibodies detected in 68.6% of total screened subjects whereas IA-2α and ZnT8A represented the single-type autoantibody detections in 5% and 2.3% of all the screened study subjects. In the same study, more than one type of autoantibody was detected in

24.1% of study subjects.[18] LADA is also sometimes referred to as T2DM with ICAs.

Besides the characteristic immune-mediated pancreatic β-cell destruction, several other autoimmune disorders including myasthenia gravis, Addison's disease (primary adrenal insufficiency), celiac sprue (celiac disease), pernicious anemia, vitiligo, Hashimoto's thyroiditis, Graves' disease, dermatomyositis, autoimmune gastritis, and autoimmune hepatitis have been observed with an increased incidence in patients with T1DM.[1,10,19,20] The autoimmune nature of this disease and its association with other autoimmune conditions mainly stem from the strong association of this disorder with human leukocyte antigen (HLA), its linkage to the DQA and DQB genes, and its direct influence by DRB genes. All of these are hotspot gene regions associated with immune response including autoimmunity. The genome-wide association studies have shown a strong association of this disease with HLA-DR3 and HLA-DR4 haplotypes and the exclusive association of DR4-DQB1I0302 haplotype with the autoimmune destruction of the β-cells. As with other diseases, these various HLA haplotypes can increase or decrease the susceptibility toward the T1DM.[21-23] However, several non-HLA genes or gene regions also influence the susceptibility to this disease. The most prominent among them is the insulin gene (INS) region, designated as IDDM2 located on chromosome 11p5.5. The variable number of tandem repeats in the promoter region of this gene region has been observed to influence the susceptibility toward this disease.[24] Besides IDDM2, CTLA-4, PTPN-22, and CD25 are other non-HLA genes associated with the disease.[25] The patients with this type of diabetes can be but are rarely obese at the time of assessment and diagnosis.[1,10]

Idiopathic diabetes

Idiopathic diabetes, also referred to as ICA-negative or type 1B diabetes, includes the forms of diabetes which are similar to T1DM in presentation but characterized by variable nonimmune β-cell dysfunction without any observed HLA association unlike T1DM and hence, sometimes it is also described as a separate type of DM. This type of diabetes exhibits a strong pattern of inheritance and has been observed in only a minority of patients, of Asian or African-Caribbean origin. The etiology of idiopathic diabetes remains largely unknown.

The disease is characterized by severe but varying degrees of insulin deficiency (insulinopenia) which can exhibit episodic patterns concomitant with varying degrees of severity and episodic DKA. These patients, therefore, may require insulin replacement therapy initially but the need for the therapy may not be absolute and may vary in accordance with the episodic patterns of insulinopenia and ketoacidosis characteristic of these forms of T1DM.[26]

Type 2 diabetes mellitus

T2DM, also known as non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, as per the previous nomenclature, constitutes about 90–95% of all the cases of diabetes. This type of diabetes is characterized by two main insulin-related anomalies: insulin resistance and β-cell dysfunction.[27-29] Insulin resistance results from disruption of various cellular pathways, which lead to a decreased response, or sensitivity of cells in the peripheral tissues, in particular the muscle, liver, and adipose tissue toward insulin. In the early stages of the disease, decreased insulin sensitivity triggers β-cells hyperfunction to achieve a compensatory increase in insulin secretion to maintain normoglycemia. The higher levels of circulating insulin (hyperinsulinemia), thus, prevent hyperglycemia. However, gradually, the increased insulin secretion by β-cells is not able to compensate sufficiently for the decrease in insulin sensitivity. Moreover, β-cell function begins to decline and β-cell dysfunction eventually leads to insulin deficiency. As a result, normoglycemia can no longer be maintained and hyperglycemia develops. Although insulin levels are decreased, the secretion of insulin in most cases is sufficient to prevent the occurrence of DKA.[29] But DKA may occur during severe stress conditions such as those associated with infections or other pathophysiological scenarios. DKA may also be precipitated by the use of certain drugs including sodium-glucose co-transporter-2 (SGLT2) inhibitors, corticosteroids, and atypical antipsychotics (second-generation antipsychotic drugs).[30,31] In absence of any severe physiological stress conditions, patients with T2DM often do not require any insulin therapy both at the time of disease onset and even after, throughout their lifetime.[27-29]

T2DM progresses very slowly and asymptomatically with even mild hyperglycemia developing over years and as such remains largely undiagnosed until the appearance of classic symptoms associated with severe hyperglycemia such as weight loss, growth impairment, blurred vision, polyuria, and polydipsia in the advanced stages of the disease. The pathogenesis/etiology of this form of diabetes is complex and involves multiple known and unknown factors, which in a conclusive manner can be described as a combination of genetic (polygenic) predispositions and strong environmental influences. T2DM has been more frequently associated with increasing age, obesity, family history of diabetes, physical inactivity, and adoption of modern lifestyles: with prior GDM in women and with pathophysiological conditions such as hypertension and

dyslipidemia. It occurs more frequently in individuals belonging to certain racial or ethnic groups including Native Americans (American Indians), Asian Americans, African Americans, Hispanic, and Latino. The frequent occurrence of T2DM in the mentioned racial or ethnic groups and its observed strong association with first-degree blood relations point strongly toward the role of genetic factors in the etiology of this disease, but these factors are complex and remain largely unspecified. However, unlike T1DM, no association of this disease has been found with genes involved in the immune response including autoimmunity and consequently there is no immune-mediated pancreatic β-cell destruction.[32,33]

Obesity plays an important role in the homeostatic regulation of systemic glucose due to its influence on the development of insulin resistance through its effect on the sensitivity of tissues to insulin and as such most but not all patients with T2DM are overweight or obese.[34] The increased body fat content, a characteristic of obesity, is such an important risk factor for T2DM that not only the total amount but also the distribution of body fat itself defines the development of insulin resistance and subsequently hyperglycemia. The increased abdominal fat or visceral obesity has been frequently associated with this type of diabetes in comparison to increased gluteal/subcutaneous fat or peripheral obesity.[35] Due to its strong association with increased body fat content or obesity, the patients with T2DM often present with various cardiovascular risk factors such as hypertension and lipoprotein metabolic abnormalities characterized by elevated triglycerides and low levels of high-density lipoproteins (HDLs). Due to its lifelong duration and associated diverse metabolic derangements characteristic of hyperglycemia, T2DM, particularly in the middle and later decades, is frequently associated with the development of various microvascular and macrovascular complications. Figure 2 enlists some of the main risk factors of T2DM.

Gestational diabetes mellitus

GDM is defined as any degree of glucose intolerance or diabetes diagnosed at the outset or during pregnancy, usually the second or third trimester. This definition earlier also included any undetected T2DM which may begin prior to or occur at the time of pregnancy onset. However, the latest recommendations of the International Association

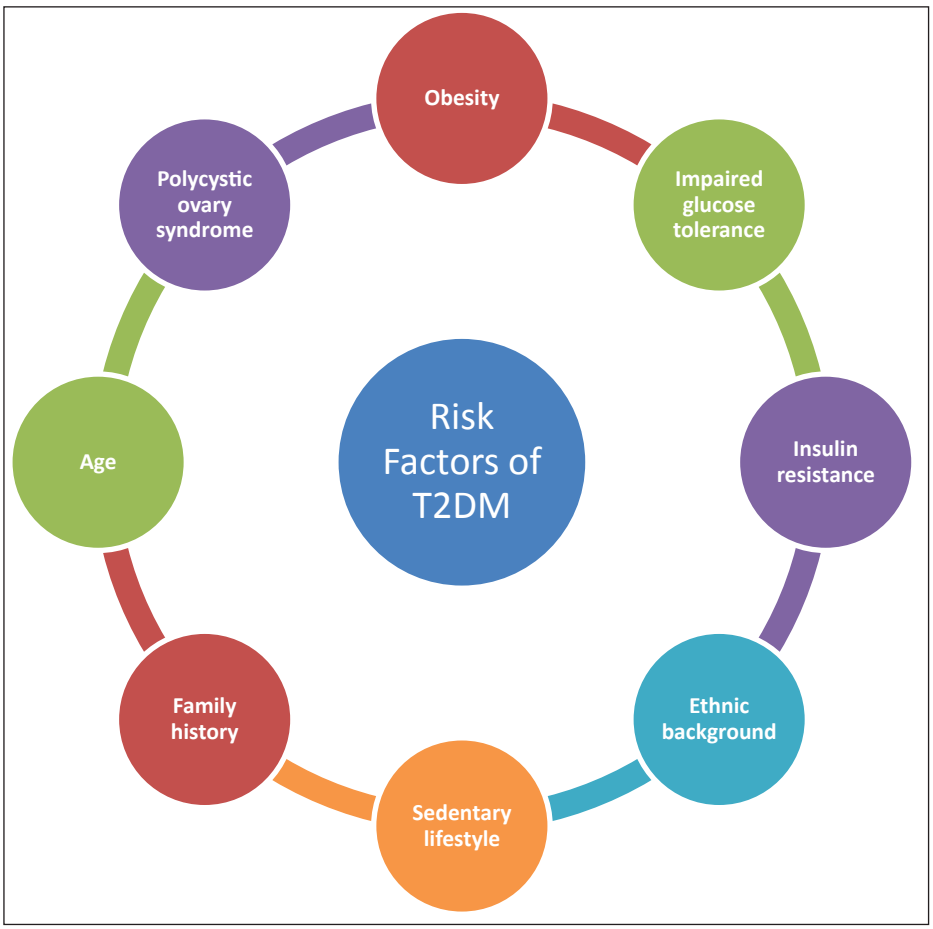

Figure 2: Some of the main risk factors of type 2 diabetes mellitus

of the Diabetes and Pregnancy Study Groups exclude from this definition diabetes diagnosed at the pregnancy onset or afterward in high-risk women such as with obesity where any degree of glucose intolerance is described as previously undiagnosed overt diabetes rather than GDM. GDM is different from any preexisting diabetes in women undergoing pregnancies and usually resolves soon after childbirth or termination of pregnancy.[1,36]

During early pregnancy, both the fasting and post-prandial blood glucose levels are usually lower than normal but the blood glucose levels increase during the third trimester of pregnancy, and in cases where this blood glucose level reaches the diabetic levels, the condition is described as GDM. More than 90% of all the cases of diabetes and its complications that occur during pregnancy can be attributed to GDM. The incidence of GDM varies from 1% to 14% of all pregnancies and its prevalence is greatly influenced by the populations under study. GDM occurs more frequently in certain racial or ethnic groups than others and this influence of ethnicity on risk of GDM is very important and has long been established. The prevalence of GDM is highest among Asian Indians, higher in aboriginal Australians, Middle Eastern (Lebanese, Syrian, Iranian, Iraqi, or Afghanistan), Filipina, Pacific Islanders, and Chinese, Japanese, Korean, and Mexican women. The prevalence is lower in blacks and lowest among non-Hispanic white women.[37,38] The risk of GDM increases with age, obesity, previous pregnancy with large babies, and any previous history of impaired glucose tolerance or GDM.[39,40] Furthermore, GDM has been associated with an increased lifetime risk of developing T2DM. The regular and lifetime screening for any kind of glucose impairment is, therefore, highly recommended in order to ensure early diagnosis of T2DM in such individuals.[41-43]

Other types of diabetes

Besides T1DM, T2DM, and GDM, diabetes in various other forms, though in smaller percentages with respect to overall diabetic incidence scenario, has been found to be associated with some specific conditions including various pathologies and/or several disorders. The prominent among these types of diabetes include diabetes resulting from the monogenic defects in β-cell function and those due to genetic abnormalities in insulin action, endocrinopathies, exocrine pancreatic pathologies, and several other specific conditions.

Diabetes caused due to the monogenic defects in β-cell function

Diabetes resulting from monogenic defects in β-cell function constitutes only 0.6–2% of all the cases of diabetes and mainly includes maturity-onset diabetes of the young (MODY) and neonatal diabetes, besides other but rare types.

Maturity-onset diabetes of the young

MODY is a genetically, metabolically, and clinically heterogeneous group of mostly non-insulin-dependent diabetes, resulting from mutations in several specific genes involved in pancreatic β-cell function, which affects glucose sensing and subsequent insulin secretion with no or minimal defects, if any, in insulin action. MODY, as the name suggests, has an early onset with glucose tolerance impairment and hyperglycemia occurring usually before the age of 25 years and is often misdiagnosed as T1DM or T2DM.[44,45] MODY accounts for less than 2% of all the cases of diabetes[46] and 1–6% of all the pediatric cases of diabetes.[47] MODY follows an autosomal dominant inheritance pattern and typically involves the vertical transmission of the disorder through at least three generations and exhibits a phenotype shared by all family members with diabetes.[48] To date, MODY has been associated with mutations in one of the 14 genes identified so far and these genes are mostly located on different chromosomes.[1,9,46,49] Figure 3 provides a graphical representation of various MODY subtypes along with their alternative names based on genes involved. The most common forms of this group of diabetes are designated as MODY2 and MODY3 which together account for more than 80% of all the cases of this type of diabetes.[50,51]

MODY2 (GCK MODY). MODY2 results from one or several of more than 200 loss-of-function mutations in the glucokinase (GCK) gene located on chromosome 7p13 and accounts for 15–25% of all MODY cases.[50,52] GCK gene codes for GCK enzyme, which catalyzes the first and rate-limiting step of glycolytic phosphorylation of glucose to glucose-6-phosphate at a rate proportional to the glucose concentration. This unique catalytic property allows the GCK enzyme to function as a sort of a glucose sensor and enables the β-cells to elicit an insulin secretion response appropriate to the existing concentrations of glucose.[53] The loss-of-function mutations characteristic of MODY2 disrupt this glucose-sensing function of the GCK enzyme such that only hyperglycemic but not normoglycemic levels can elicit a normal insulin secretion response from the β-cells. In MODY2, the fasting hyperglycemia remains mild but persistent and stable and the disorder is non-insulin-dependent. MODY2 is clinically nonprogressive with mild or no symptoms and is usually not associated with the development of microvascular and macrovascular complications. GCK gene is a mutational hotspot region and more than 600 mutations have been identified in the 10 exons of this gene, which have been associated with both hyperglycemia and hypoglycemia.[54]

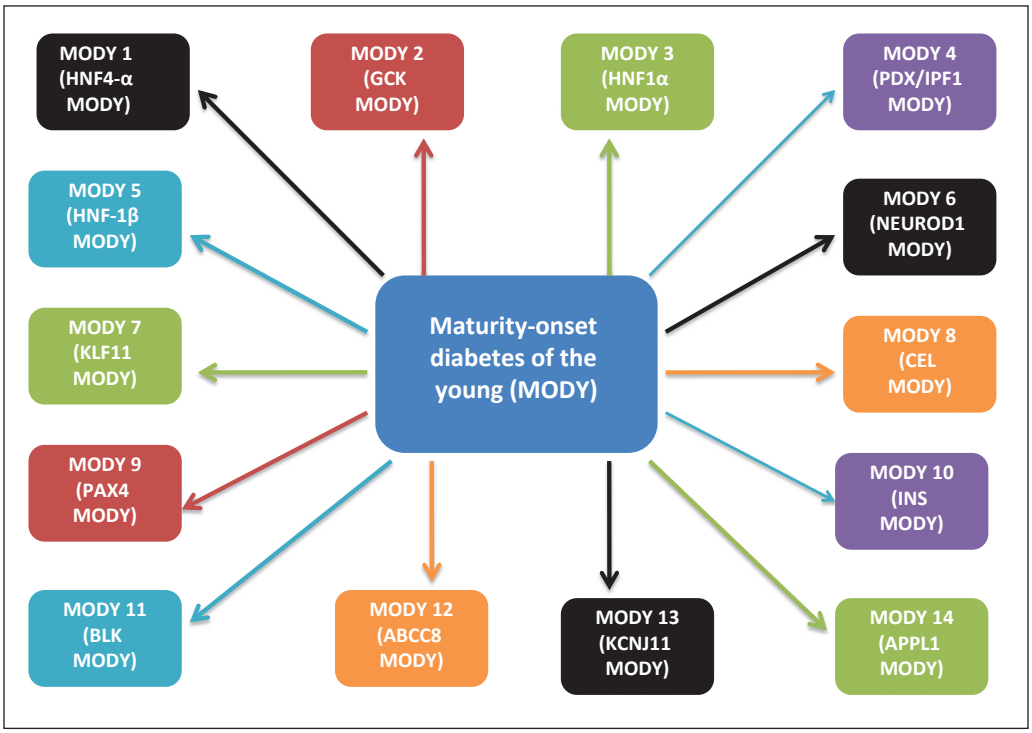

Figure 3: Types of maturity-onset diabetes of the young and their alternative names based on genes involved

MODY3 (HNF-1α MODY) and MODY1 (HNF-4α MODY). MODY3 results from the loss-of-function mutations in hepatocyte nuclear factor (HNF)-1α gene located on chromosome 12q24, which codes for the transcription factor, HNF-1α (transcription factor MODY) and accounts for 30–50% of all MODY cases.[51] HNF-1α is expressed in the kidney, liver, intestine, and pancreatic β-cells and is involved in regulating the expression of several hepatic genes many of which are involved in glucose metabolism including glucose transporter 1 and 2 (GLUT1 and GLUT2). More than 400 mutations have been identified in HNF-1α gene.[55] MODY3 presents with a symptomatic rapid progression to overt diabetes reflected through a progressive impairment from glucose intolerance to severe hyperglycemia, often leading to T1DM and T2DM like microvascular and macrovascular complications. MODY3 has been associated with a decreased pancreatic β-cell mass due to an increased rate of β-cell apoptosis, particularly from the third decade of life onward, and therefore, MODY3 is characterized by a progressive decrease in insulin secretion.[56] Depending on the hyperglycemic severity and duration since onset, MODY3 may be or may not be insulin-dependent.

MODY1 accounts for around 5% of all MODY cases. MODY1 is caused due to the loss-of-function mutations in the transcription factor, HNF-4α gene located on chromosome 20q13. HNF-4α is mainly expressed in the liver and also in kidney and pancreatic β-cells and regulates the expression of genes involved in glucose transport, metabolism, and nutrient-induced insulin secretion and also triglyceride metabolism and lipoprotein biosynthesis.[57] HNF-4α mutation is characterized by a progressive defect and a decline in insulin secretion from infancy onward and resembles clinically with MODY3. It is associated with hyperinsulinemic hypoglycemia in the neonatal period, which begins to remit during infancy, and as such, the decline in insulin production starts in infancy but the emergence of hyperglycemia and subsequent full-blown diabetes occurs during adolescence.[47,58] HNF-4α mutation and hence MODY1 have been associated with decreased levels of apolipoprotein—apoAII, apoCIII, and apoB and HDLs and increased levels of low-density lipoproteins (LDLs).

Hyperglycemia associated with HNF-1α and HNF-4α mutations in MODY3 and MODY1, respectively, can be efficiently controlled through the treatment with low-dose sulfonylureas. These agents maintain efficacy or remain effective for many years and are preferred first-line of treatment in these patients compared to insulin and other therapies used in T1DM and T2DM. However, to ensure proper treatment, an early and accurate diagnosis is very important to avoid mislabeling these MODY types as T1DM or T2DM and prevent administration of inappropriate avoidable therapies in these patients.[59,60]

MODY5 (HNF-1β MODY). MODY5 results from mutations in the transcription factor, HNF-1β gene located on

chromosome 17q12 and accounts for around 5% of all cases of MODY.[61,62] HNF-1β is involved in the regulation of genes that are associated with various embryonic developmental processes, in particular, the genesis of various organs including the liver, pancreas, lungs, gut, kidney, and genitourinary tract.[63] MODY5 develops in early adolescence or adulthood. HNF-1β mutations that result in MODY5 often present as renal cysts, renal cysts and diabetes syndrome, renal dysplasia, hypoplastic glomerulonephritic kidney disease, urinary tract malformation,[64,65] and reduced birth weight.[66] Some of these conditions are evident from the 17th week of gestation[65] or are seen in infants or young children, independent of the hyperglycemic status.[47] Renal dysfunction,[65] liver dysfunction, and pancreatic abnormalities[67] are common as the disorder develops and end-stage renal disease develops in half of the patients with MODY5 by 45 years of age independent of diabetic kidney disease status.[65] Genitourinary tract malformations especially uterine abnormalities such as rudimentary uterus in addition to vaginal aplasia have also been reported in MODY5.[67] Insulin dependence develops relatively earlier due to liver and pancreatic abnormalities, in particular, hepatic insulin resistance and pancreatic hypoplasia.[47,68] Hyperuricemia, gout, low HDL levels, and elevated triglyceride levels are commonly observed in patients with MODY5.[61,69]

Other types of MODY. Relatively rare and less common types of MODY, which account for less than 1% of all MODY cases, include as follows:

MODY4 (PDX-1/IPF-1 MODY): MODY4 results from mutations in the transcription factor, pancreatic and duodenal homeobox-1(PDX-1), also known as insulin promoter factor (IPF)-1 gene located on chromosome 13q12.2.[70] PDX-1/IPF-1 is involved in the development of exocrine and endocrine pancreas and plays an important role in regulating the expression of insulin, glucagon, GLUT2, and GCK encoding genes.[71,72] Homozygous mutations in PDX-1/IPF-1 gene result in pancreas agenesis, hypoplasia, and pancreatic exocrine insufficiency and in permanent neonatal diabetes (PND) whereas heterozygous PDX-1/IPF-1 gene mutations cause β-cell impairment, which leads to defective insulin secretion and hyperglycemia.[73,74]

MODY6 (NEUROD1 MODY): MODY6 results from mutations in the transcription factor, neurogenic differentiation factor-1(NEUROD1) gene located on chromosome 2q31.[75] NEUROD1 belongs to the basic helix-loop-helix family of transcription factors and is involved in the regulation of several cell differentiation pathways associated with neuronal and pancreatic development, in particular, those involved in endocrine islet cells (islets of Langerhans) differentiation including the pancreatic β-cells. NEUROD1 gene mutations interfere with the maturation of β-cells and impair their glucose-sensing ability and as a result, their insulin secretion response. Homozygous NEUROD1 gene mutations lead to neonatal diabetes and are associated with neurological abnormalities whereas heterozygous mutations result in childhood- or adult-onset diabetes.[76,77]

The other types of MODY in this category include MODY7 (KLF11 MODY), which results from the mutations in Kruppel-like factor 11 (KLF11) gene located on chromosome 2p25[78] and MODY8 (CEL MODY), which arises from the mutations in carboxyl ester lipase (CEL) gene located on chromosome 9q34.[79] This category also includes MODY9 (PAX4 MODY), caused due to the mutations in PAX family transcription factor, Paired box gene 4 (PAX4) gene located on chromosome 7q32[80] and MODY10 (INS MODY), which results from the mutations in the INS located on chromosome 11p15[81,82]; also, MODY11 (BLK MODY), which arises due to the mutations in the human homolog of a B-lymphocyte-specific protein tyrosine kinase (BLK) gene located on chromosome 8p23.1.[83]

Furthermore, there is MODY12 (ABCC8-MODY), which results from the mutations in ATP-binding cassette transporter subfamily C member 8 (ABCC8) gene located on chromosome 11p15 and ABCC8 which encodes sulfonylurea receptor-1 (SUR1) protein, a subunit of ATP-sensitive potassium (KATP) channel. MODY12 is responsive to sulfonylureas.[84]

The remaining types include MODY13 (KCNJ11-MODY) and MODY14 (APPL1-MODY). MODY13 (KCNJ11-MODY) is caused due to the mutations in potassium inwardly rectifying channel subfamily J member 11 (KCNJ11) gene located on chromosome 11p15.1 which encodes β-cell inward rectifier, BIR (inwardly rectifying potassium channel Kir6.2), a subunit of ATP-sensitive potassium (KATP) channel.[85,86] MODY14 (APPL1-MODY) results from the mutations in Adaptor Protein, Phosphotyrosine Interacting With PH Domain and Leucine Zipper 1 (APPL1) or DCC-interacting protein 13-α (DIP13-α) gene located on chromosome 3p14.3.[87]

Neonatal diabetes mellitus

Neonatal diabetes mellitus (NDM), also known as early-onset or congenital diabetes, is the diabetes diagnosed during the first 6 months of life. It is a rare disorder with a global incidence rate of 1 per 500,000–300,000 (1:500,000–1:300,000)[88,89] live births; though a study in Italy has reported a higher incidence of 1 per 90,000

(1:90,000).[88] NDM is predominantly of genetic origin with 80–85% cases occurring due to monogenic defects and is characterized by severe uncontrolled hyperglycemia along with hypoinsulinemia and requires insulin replacement therapy.[89] The genetic abnormalities lead to β-cell dysfunction and decreased β-cell mass due to increased apoptotic or non-apoptotic β-cell death. These defects also result in developmental abnormalities of pancreas and/or its islets or in very rare cases their complete absence leading to decreased production and secretion of insulin or hypoinsulinemia and in the latter case an absolute insulin deficiency.[90] Neonatal diabetes is highly distinct from early-onset T1DM and differs from it both in the origin and pattern of inborn pancreatic disorder and mostly occurs during the first 6 months of life whereas T1DM mostly develops after 6 months of life. Based largely on the clinical features, NDM can assume either of these two forms: transient neonatal diabetes mellitus (TNDM) and permanent neonatal diabetes mellitus (PNDM).

TNDM is the more common form representing approximately 55–60% of all cases of neonatal diabetes. It usually resolves within 12–18 months after birth but in a majority of cases, NDM relapses during the later years of life from late childhood to early or late adulthood and presents itself as T2DM, indicating the presence of varying degrees of severity, but persistent β-cell dysfunction, which leads to possible inadequate insulin secretion and/or insulin resistance. Furthermore, the diabetes may also precipitate under stress conditions such as hormonal changes as observed in puberty or in certain diseases.[89,91] TNDM results most often from the abnormalities in chromosome 6 specifically involving the overexpression of imprinted and paternally expressed genes in the 6q24 region. This includes the HYMAI (hydatiform mole associated and imprinted) gene, zinc finger protein, ZAC gene, and pituitary adenylate cyclase activating polypeptide-1 (PACAP1) gene. A small percentage of TNDM cases arises from the mutations in the ATP binding cassette subfamily C member 8 (ABCC8) gene also known as sulfonylurea receptor-1 (SUR1) gene and rarely from the mutations in the potassium voltage-gated channel subfamily J member 11 (KCNJ11 or Kir6.2).[89] Both ABCC8 and KCNJ11genes are functionally linked together as these genes encode for the proteins that constitute the individual subunits of the β-cell K_{ATP} channel. The K_{ATP} channel is an eight-subunit ATP-sensitive potassium channel with two types of subunits: four regulatory subunits encoded by ABCC8 (SUR1) gene and four pore-forming subunits encoded by KCNJ11 (Kir6.2) gene. This channel regulates the secretion of insulin from the pancreatic β-cells, thus providing a direct link with normal glucose homeostasis and its dysregulation in diabetes.

PNDM is the less common form of NDM, which unlike TNDM does not go into remission and persists permanently. PNDM most commonly results from the heterozygous autosomal dominant mutations in the ABCC8 and the KCNJ11 genes encoding, respectively, the SUR1 and Kir6.2 subunits of the β-cell K_{ATP} channel.[9,89] Several mutations identified in the INS also cause PNDM.[9] Besides, this type of neonatal diabetes is associated with several syndromes including the immune-dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, and Wolcott–Rallison syndrome. IPEX syndrome is an autoimmune disorder that results from the mutations in the FOXP3 gene. The autoimmune disorders that characterize IPEX syndrome include autoimmune enteropathy (an autoimmune disorder of the intestines), dermatitis or eczema (an autoimmune disorder of the skin), and polyendocrinopathy (multiple autoimmune disorders of the endocrine glands, including pancreas and thyroid).[9,89,92] WRS is an autosomal recessive disorder, which results from the mutations in the EIF2AK3 gene.[9,89,93] The main characteristics of this disorder include multiple epiphyseo-metaphyseal dysplasia and hepatic dysfunction. Diabetes is a permanent feature associated with this syndrome and in consanguineous families; WRS has emerged as the most frequent cause of PNDM.[94,95] Clinically, it is not possible to predict whether a particular neonatal dysfunction of glucose homeostasis will eventually develop into TNDM or PNDM, which makes the correct diagnosis, and the assessment of the underlying cause of the disorder including the genetic factors involved, an important aspect in the management of this disorder.

Besides MODY and NDM, there are several other monogenic defects in β-cell function which result in DM. These include the point mutations in mitochondrial DNA such as 3243A-G mutation in the mitochondrial transfer RNA leucine-1 (MTTL1) gene, which leads to deafness and diabetes[96] and the autosomal dominant mutations, which result in a total inability or abnormal conversion of proinsulin to insulin.[97] Furthermore, it also includes the mutations that lead to the production of structurally abnormal insulin molecules with impaired receptor binding.

Diabetes caused due to genetic abnormalities in insulin action

Several genetic abnormalities in insulin action resulting either from insulin receptor functional impairment or decrease in the number of insulin receptors, caused mainly due to the mutations in insulin receptor (INSR) gene located on chromosome 19, have been identified. These abnormalities in insulin action lead to hyperinsulinemia or insulin resistance and subsequent mild to modest hyperglycemia or may even cause severe hyperglycemia

characteristic of overt diabetes.[1] The various forms of diabetes resulting from the abnormalities in insulin action, often described as inherited severe insulin resistance syndromes, include type A insulin resistance syndrome, lipoatrophic diabetes, Donohue syndrome (leprechaunism), and Rabson–Mendenhall syndrome (RMS).

Type A insulin resistance syndrome results from mutations in INSR gene. This syndrome is associated with menstruation disorders (primary amenorrhea or oligomenorrhea) and specific forms of polycystic ovarian syndrome characterized by hirsutism due to hyperandrogenism and multiple enlarged cysts on the ovaries, in females[98]; also, acanthosis nigricans, a skin pigmentation disorder, most often in females than in males[99] and obesity,[100] most often in males than in females and severe insulin resistance.

Lipoatrophic diabetes is a monogenic but heterogeneous insulin resistance syndrome associated with lipoatrophy and lipodystrophy and characterized by paucity (insufficiency) of fat, insulin resistance, and dyslipidemia, more specifically, hypertriglyceridemia.[101] Lipoatrophic diabetes arises due to the mutations in several different genes, which manifests as different genetic syndromes. It may result from the mutations in Laminin A/C (LMNA) gene located on chromosome 1q21–22 and manifest as an autosomal dominant disorder known as familial partial lipoatrophy, also known as Dunnigan or Koberling-Dunnigan syndrome.[102] Lipoatrophic diabetes may also result from the mutations, either in the AGPAT2 gene or in the BSCL2 gene. AGPAT2 gene located on chromosome 9q34 encodes the enzyme 1-acyl-sn-glycerol-3-phosphate-D-acetyltransferase-2, which is involved in triglyceride synthesis. Berardinelli-Seip congenital lipodystrophy type-2 (BSCL2) gene, also known as γ3-linked gene (GNG3) or seipin gene, located on chromosome 11q13 encodes seipin, an endoplasmic reticulum-associated protein involved in lipid droplet biogenesis. Both these mutations manifest as an autosomal recessive disorder known as Congenital generalized lipoatrophy or Berardinelli-Seip syndrome.[103,104]

Furthermore, the mutations in insulin receptor gene may also lead to the Donohue syndrome (leprechaunism) and the RMS, both of which manifest in infancy, and diabetes in these syndromes is characterized by strong insulin resistance and severe hyperglycemia.[105]

Endocrinopathies

Several endocrinopathies resulting in or from abnormal functioning of various hormones can lead to diabetes. These include the endocrinopathies that involve the hyperactivity of those hormones which partly or fully antagonize the function of insulin such as Cushing syndrome, acromegaly, pheochromocytoma, glucagonoma, and hyperthyroidism, which result from hyperactivity of cortisol, growth hormone, norepinephrine (and epinephrine), glucagon, and thyroid hormones, respectively. Diabetes associated with these endocrine disorders usually occurs when a defect in insulin secretion and/or action is already present.[106,107] Some endocrinopathies induce diabetes through inhibition of insulin secretion and these include somatostatinoma, which leads to the excessive secretion of somatostatin and primary hyperaldosteronism[108] or Conn's syndrome induced hypokalemia, which involves the hypersecretion and hyperactivity of the hormone, aldosterone.[109] Diabetes caused due to various endocrinopathies usually resolves when endocrinopathies are treated or managed.

Exocrine pancreatic pathologies

Several diseases of the exocrine pancreas have been found to cause diabetes but the contribution of these diseases to the overall incidence of diabetes is minimal with less than 0.5% of all the cases of diabetes resulting from the diseases of the exocrine pancreas. These include chronic pancreatitis (fibrocalculous pancreatopathy), trauma (pancreatectomy), infection, hereditary hemochromatosis, secondary hemochromatosis, cystic fibrosis, and pancreatic neoplasia (adenocarcinoma and glucagonoma).[110-112] All these pancreatic pathologies, with the exception of pancreatic neoplasia, lead to diabetes only when they are severe enough to cause extensive pancreatic damage, involving the endocrine pancreas, including the islets of Langerhans, which leads to a considerable reduction in the β-cell mass and impairment of β-cell function.[113] The pancreatic neoplasia-associated diabetes occurs even without any reduction in β-cell mass.[1]

Infections

Several infections caused by viruses are known to cause β-cell dysfunction, mainly through β-cell destruction, and lead to hyperglycemia, which gradually presents as overt diabetes. These include infections caused by cytomegalovirus, adenovirus, Coxsackie virus B, and mumps. Besides, congenital rubella syndrome, caused by rubella virus, has also been closely linked with diabetes, but this diabetes in most of the cases is associated with the presence of HLA and other immune markers, which are characteristic of T1DM.[1,114,115] Furthermore, insulin resistance has been associated with chronic hepatitis C virus infection and progression of fibrosis and a very high prevalence of T2DM has been reported among the individuals infected with the hepatitis C virus.[116,117]

Drug- or chemical-induced

Several drugs and chemicals are known to induce diabetes. These agents induce diabetes either through the impairment of insulin production or secretion, which mainly results from the destruction of β-cells or through a decrease in the sensitivity of tissues to insulin, which causes insulin resistance. Diabetes resulting from the drug- or chemical-induced increase in insulin resistance occurs only in susceptible individuals. Furthermore, these agents may worsen or increase the severity of hyperglycemia in individuals with already existing overt diabetes. The drugs and chemicals known to induce diabetes include glucocorticoids, diazoxide, thiazides, β_2-receptor agonists (salbutamol and ritodrine), nonselective β-adrenergic antagonists, dilantin, hormones including growth hormone (in very high doses), thyroid hormone (thyroxine/triiodothyronine), somatostatin, estradiol, levonorgestrel, and glucagon. These also include γ-interferon, protease inhibitors (indinavir, nelfinavir, ritonavir, and saquinavir), nicotinic acid, and β-cell toxins including streptozocin (streptozotocin), cyclosporine, rodenticide vacor and pentamidine, and several antipsychotics.[118,119] Furthermore, immune checkpoint inhibitors, such as ipilimumab, nivolumab, and pembrolizumab, used in cancer immunotherapy for treatment of advanced-stage cancers, including head and neck cancer, renal cancer, urothelial cancers, non-small-cell lung carcinoma, and melanoma besides other cancers[120-125] have been reported to induce new-onset T1DM, through immune-mediated β-islet cell dysfunction.[125,126]

Other genetic syndromes associated with diabetes

There are many others, besides the already mentioned genetic syndromes, that are usually associated with an increased incidence of diabetes. These include Down's syndrome, Turner's syndrome, Wolfram's syndrome, Klinefelter's syndrome, Huntington's chorea, Friedreich's ataxia, myotonic dystrophy, Laurence-Moon-Biedl syndrome, Porphyria, and Prader-Willi syndrome among others.[127]

Uncommon forms of immune-mediated diabetes

The uncommon forms of immune-mediated diabetes are very rare in occurrence and mainly include diabetes associated with Moersch-Woltman syndrome (stiff-person syndrome [SPS]), anti-insulin receptor antibodies (AIRAs), and insulin autoimmune syndrome (IAS; Hirata's disease).

Moersch-Woltman syndrome or the SPS is a very rare autoimmune disorder that affects the central nervous system and is characterized by progressive fluctuating rigidity of the axial muscles (muscles of the trunk and head), accompanied by painful muscle spasms. Patients with SPS generally present with high titers of GADAs and are frequently associated with various diseases including pernicious anemia, thyroiditis, vitiligo, and type 1-like diabetes. Although GADAs are detected in most of the individuals with T1DM alone; but the individuals with SPS with or without diabetes have 50–100 times more titers of GADAs.[128]

The AIRAs are often associated with various autoimmune diseases, including primary biliary cholangitis, systemic lupus erythematosus, and Hashimoto thyroiditis. AIRAs generally bind to insulin receptors on various insulin target tissues, which block the binding of insulin to these receptors and hence the subsequent signaling pathways. This leads to diabetes characterized by a rapidly progressive and extreme form of insulin resistance, earlier termed as type B insulin resistance. Alternatively, AIRAs once bound to target receptors may sometimes cause spontaneous hyperinsulinemic hypoglycemia by acting as insulin agonists. Diabetes associated with AIRAs is often characterized by acanthosis nigricans and impaired insulin degradation.[129,130]

IAS or Hirata's disease is described as a condition, which is characterized by the presence of autoantibodies to the endogenous insulin (IAA) in the absence of any previous exposure to the exogenous insulin, absence of any pathological abnormalities of the pancreatic islets and presents as endogenous hyperinsulinemia hypoglycemia. Although, the predisposition to this condition is present from birth, but the overt disease most often presents itself during adulthood and can be triggered by exposure to certain drugs and viruses. IAS can be controlled through simple dietary management.[131]

Ketosis-prone diabetes mellitus

Ketosis-prone diabetes mellitus (KPD) describes another heterogeneous group of diabetes, which like T2DM, characteristically does not involve the immune-mediated destruction of pancreatic β-cells but unlike T2DM, this type presents with frequent episodes of DKA or unprovoked ketosis.[132] KPD occurs most frequently in African Americans and Africans in sub-Saharan Africa but has now been observed increasingly in Hispanic, Chinese, and Japanese populations.[132-135] One of the best described subtypes of this diabetes is Flatbush diabetes which along with characteristic episodic DKA is frequently associated with HLA-DR3 and/or HLA-DR4 haplotypes.[136] The patients with KPD show periodic but absolute requirement of insulin replacement therapy, concomitant with the episodes of DKA and outside of the frequent episodes of DKA, the diabetes can be controlled through simple diet management without insulin replacement therapy.

CONCLUSIONS

DM is a heterogeneous metabolic disease, represented by diverse forms, each with a distinct pathophysiological origin but often manifest as a disorder with overlapping and difficult-to-differentiate characteristics. The treatment and management of each of these diabetic types are distinct in some characteristics but share a great deal of similarity as well as is the case with the disorder itself. All this emphasizes the importance of correct and timely diagnosis of each of these diabetic types and the critical role of their pathophysiological understanding. This is vital to safeguard diabetic individuals from exposures to potential adverse effects of improper, ineffective, or avoidable pharmaceutical interventions, which often delays the desired prognosis and increases the duration of hyperglycemic exposures. The long-term hyperglycemia, in turn, has often been associated with increased risk of microvascular and macrovascular diabetic complications, which affect the quality of life and mainly contribute to the diabetes-associated morbidity and mortality. For diabetes in general, and in particular, the diabetes types resulting from genetic mutations or associated genetic anomalies, the correct and timely molecular diagnosis can help in disease risk analysis and help in disease prediction and timely identification of individuals at an increased risk to the disorder, in particular, the family members. The predictive molecular/genetic testing and preventive management can play a vital role in such cases. Furthermore, irrespective of the diabetes type, various lifestyle modifications and interventions such as extensive diet control, physical exercises, change of daily sedentary routine, and control of obesity are important in the prevention and the management of diabetes. The educational campaigns, which make the general population aware of the pathogenesis of this disease and the various controllable risk factors associated with it, are also a vital tool in the management and control of diabetes mellitus.

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Conflict of interest

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