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Diabetes Mellitus: Classification, Pathophysiology, Risk Factors, Diagnostic Criteria and Advances in Management

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ABSTRACT

Diabetes mellitus (DM) is a rapidly growing chronic disease, driven by defects in insulin secretion, insulin action or both. Insulin action refers to the hormone's ability to facilitate glucose uptake by cells. Insulin enables glucose uptake in muscle and fat cells while inhibiting liver glucose production. DM affects approximately 8.5% of the global population, with projected growth to 10.9% by 2030, placing a considerable burden on healthcare systems worldwide. It is significantly contributing to global morbidity and mortality The complex and multifaceted nature of DM, involving genetic, environmental and lifestyle factors, underscores the need for focused research.

This is a compressive type of review provides an overview of DM, encompassing its classification, pathophysiological mechanisms, risk factors, diagnostic criteria management, Pharmacological Treatment and advances in diabetes. Additionally, in this review various forms of diabetes is covered, including detailed information about Type 1 diabetes mellitus(T1DM), Type 2 diabetes mellitus(T2DM), gestational diabetes mellitus (GDM), and less common forms such as Latent Autoimmune Diabetes in Adults (LADA), Maturity Onset Diabetes of the Young (MODY), Maternally Inherited Diabetes and Deafness (MIDD) and Neonatal Diabetes Mellitus (NDM).

The review highlights pharmacological treatments for DM, including oral medications like metformin, sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors, TZDs, insulin therapy and newer agents like GLP-1 receptor agonists, discussing their efficacy, side effects and combination therapies. It also covers advances in diabetes management, such as gene therapy, immunotherapy, stem cell research and technologies like artificial pancreas systems and continuous glucose monitors (CGMs), aimed at improving patient outcomes. The importance of early diagnosis, comprehensive treatment, and ongoing research to address the global burden of DM is emphasized.

1. INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases that disrupt the metabolism of carbohydrates, lipids, and proteins [1]. The American Diabetes Association (ADA) defines DM as a group of metabolic disorders characterized by chronic hyperglycemia (high blood sugar). This hyperglycemia results from defects in insulin secretion, insulin action or a combination of both. Insulin action specifically refers to the body's ability to use insulin effectively to facilitate glucose uptake by cells and regulate blood glucose levels. In DM, impairments in insulin action may include insulin resistance, where cells do not respond appropriately to insulin, leading to insufficient glucose uptake and elevated blood sugar levels [2]. Persistent hyperglycemia in DM is associated with long-term damage and dysfunction of various organs. Specific complications include diabetic retinopathy (damage to the eyes), diabetic nephropathy (kidney damage), diabetic neuropathy (nerve damage) and cardiovascular diseases such as coronary artery disease (heart damage) and peripheral vascular disease (damage to blood vessels) [3]. Typically, significant organ damage may develop within 5 to 10 years from the onset of diabetes, although this can vary based on individual factors such as glycemic control and overall health. Early and effective management of blood glucose levels is crucial in delaying or preventing these complications [4].

DM is one of the fastest-growing and most common illnesses worldwide, affecting approximately 8.5% of the global population. This burden is particularly severe in low and middle-income countries. Each year, diabetes is directly responsible for 2.5% of global deaths [5]. A significant portion of these deaths, around 48%, occurs in individuals under the age of 70.

In addition to direct mortality, DM contributes to an estimated 30.7% of deaths from kidney disease and is implicated in 20% of cardiovascular disease related deaths due to elevated blood glucose levels. The mechanisms of direct mortality from diabetes include cardiovascular complications, where chronic high blood glucose accelerates atherosclerosis, leading to heart attacks and strokes; diabetic ketoacidosis (DKA), resulting from insufficient insulin, which can cause severe metabolic acidosis, coma or death; and chronic hyperglycemia, which damages the kidneys and leads to end-stage renal disease. Diabetes also increases susceptibility to severe infections due to impaired immune function and poor wound healing. Additionally, severe hypoglycaemia from insulin or medication can cause seizures, loss of consciousness and death [6]. Globally, the prevalence of diabetes has been steadily rising. In 2010, about 6.4% of the global adult population had diabetes, and by 2014, this prevalence had increased to 8.5%. Without significant improvements in control and treatment, the number of people affected by diabetes is projected to rise intensely. The International Diabetes Federation (IDF) predicts that the global prevalence of diabetes will increase from 8.4% in 2011 to 10.9% by 2030. Also, prediabetes affected approximately 9.1% of the global population in 2021 [7,8].

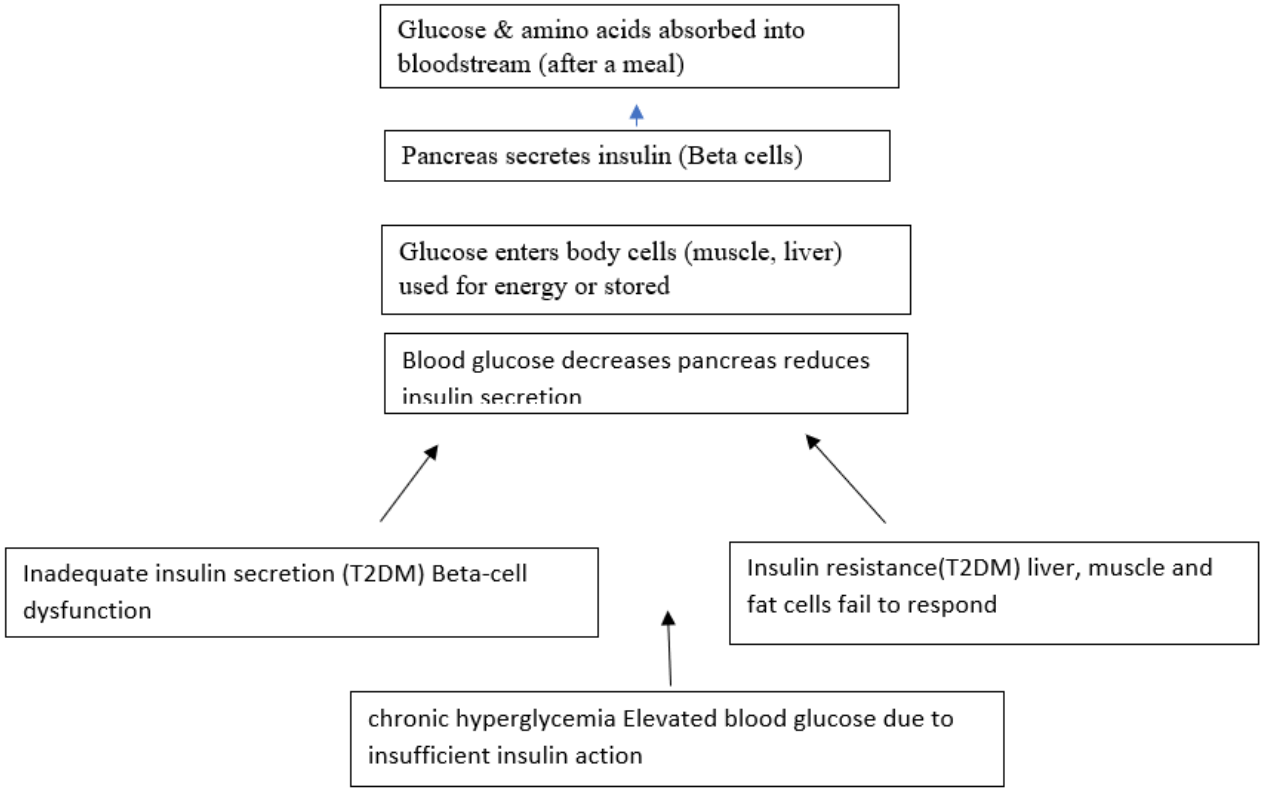
Gestational diabetes mellitus (GDM) affects around 14% of pregnancies globally, posing significant risks to both maternal and fetal health. Additionally, the IDF estimated in 2019 that the global prevalence of impaired glucose tolerance (IGT) was 7.5% in both men and women [9].

Pathophysiology of Diabetes

The pancreas plays a vital role in regulating the body's glucose levels, by secreting digestive enzymes and hormones, like insulin and glucagon, into the bloodstream [10]. Insulin assists in lowering blood sugar levels by enabling glucose (simple sugars from food) to enter body cells, where it is metabolized [11]. In contrast, if blood glucose levels fall too low, the pancreas releases glucagon, which prompts the liver to release glucose from its stores into the bloodstream [12]. Following a meal, glucose and amino acids are quickly absorbed into bloodstream, leading to a sharp increase in blood glucose levels [13]. This spike triggers the pancreatic beta cells, within the pancreas, to secrete insulin, which floods the bloodstream approximately 20 minutes after the meal [14]. Insulin facilitates the uptake of glucose by body cells, particularly muscle and liver cells, where it is either burned for energy or stored for later use [15]. When insulin levels are high, the liver stops producing glucose and instead stores it in other forms until the body needs it again [16]. Typically, about two to four hours after a meal, both insulin and blood glucose levels reach their lowest points. As blood glucose levels decrease, the pancreas adjusts by decreasing insulin production [17].

Diabetes can result from two primary dysfunctions: inadequate insulin secretion by pancreatic β-cells and the failure of insulin-sensitive tissues to respond properly to insulin. Inadequate insulin secretion by pancreatic β-cells is often caused by β-cell dysfunction, where the β-cells in the islets of Langerhans fail to produce enough insulin in response to elevated blood glucose levels. This dysfunction can arise due to genetic predisposition, environmental factors or chronic metabolic stress [18]. Chronic hyperglycemia and an increased demand for insulin can also lead to β-cell exhaustion and apoptosis, ultimately reducing the number of functional insulin-secreting cells over time [19].

Insulin resistance in peripheral tissues, including muscle, fat and liver cells, also plays a critical role in T2DM. In T2DM, muscle and fat cells become resistant to insulin, impairing their ability to uptake glucose from the bloodstream, which contributes to elevated blood glucose levels [20]. The liver's resistance to insulin exacerbates the condition by leading to inappropriate glucose production and release into the bloodstream, further worsening hyperglycemia [21].



Glucose Regulation and Diabetes mechanisms

Diabetes Mellitus Risk Factors:

Non-Modifiable Risk Factors

Family history, race, age and GDM are significant risk factors for prediabetes and T2DM. Individuals with a family history of diabetes, particularly those with first-degree relatives affected, aspect an increased risk, with the risk being even higher if both parents have T1DM. Additionally, certain ethnic backgrounds, such as American, Asian, Hispanic, Native American or Pacific Islander, are more prone to arising diabetes due to a combination of genetic, environmental and lifestyle factors [22]. The risk of T2DM also increases with age especially after 45, while T1DM typically develops in children and younger adults [23].

Modifiable Risk Factor

Overweight and obesity increase the chance of getting diabetes due to insulin resistance, which be evaluated using the body mass index and waist circumference [24]. Physical inactivity is a significant risk factor for prediabetes and T2DM, as regular physical activity helps control body weight, regulate blood glucose levels and improve insulin sensitivity [25]. High blood pressure, often resulting from untreated hypertension, can lead to complications such as heart disease and diabetes. Smoking and excessive consumption of alcohol also contributes to insulin resistance and inflammation, both of which are key factors in the development of T2DM [26]. Smoking increases the risk of T2DM, while heavy alcohol consumption may lead to pancreatitis and impair insulin secretion. Excessive intake of sugary beverages also contribute to T2DM by promoting weight gain, insulin resistance and metabolic disturbances [27]. poor diet, high in refined sugars, saturated and trans fats and low in fiber, further increases the possibility of diabetes [28]. Lastly dyslipidemia, characterized by abnormal cholesterol and triglyceride levels, is closely associated with a higher chance of diabetes [29].

Diagnosis of Diabetes Mellitus (DM)

The diagnosis of DM is primarily based on established criteria from organizations such as the American Diabetes Association (ADA) and the World Health Organization (WHO). Several standard tests are used to assess blood glucose levels, each with unique characteristics:

Fasting Plasma Glucose Test (FPG):

After a night of fasting, the FPG test measures blood glucose; a result of ≥126 mg/dL (7.0 mmol/L) indicates diabetes. With a high specificity of approximately 90–95% and minimal false positives, the FPG test is easy to use and cost-effective. However, its sensitivity (~70-80%) means certain diabetes cases might go unnoticed [30].

Oral Glucose Tolerance Test (OGTT):

The OGTT, which involves administering a 75-gram glucose load and measuring plasma glucose two hours later, is a more comprehensive test. A 2-hour plasma glucose level of ≥200 mg/dL (11.1 mmol/L) indicates diabetes. The OGTT has a higher sensitivity (~80-90%) than the FPG, making it particularly useful for diagnosing GDM and in cases where FPG results are unclear. However, it is more complicated and necessitates fasting, which can be inconvenient [31].

Random Plasma Glucose Test:

The Random Plasma Glucose Test is another option, measuring glucose levels without fasting. A random plasma glucose level ≥200 mg/dL (11.1 mmol/L) along with classic hyperglycemia symptoms confirms a diagnosis of diabetes [32].

Hemoglobin A1c (HbA1c):

The HbA1c test measures average blood glucose over the past 2–3 months, with an HbA1c level ≥6.5% (48 mmol/mol) diagnosing diabetes. This test is particularly useful for long-term glucose monitoring, as it does not require fasting. However, HbA1c has a lower sensitivity (~60-70%) than FPG and OGTT, and its results can be affected by conditions like anemia or hemoglobinopathies, making it less reliable in certain populations [33].

Diagnosis of Prediabetes

Prediabetes is diagnosed when blood glucose levels are elevated but not high enough to meet the criteria for diabetes. It can be classified as either Impaired Fasting Glucose (IFG), with FPG levels between 100–125 mg/dL (5.6–6.9 mmol/L), or Impaired Glucose Tolerance (IGT), where 2-hour OGTT results range from 140–199 mg/dL (7.8–11.0 mmol/L). [34]

Gestational Diabetes Mellitus (GDM)

GDM is usually diagnosed using one of two methods between weeks 24 and 28 of pregnancy. The diagnosis criteria for the 1-step approach are 75g OGTT, with diagnosis based on FPG ≥5.1 mmol/L, 1-hour glucose ≥10.0 mmol/L, or 2-hour glucose ≥8.5 mmol/L. The 2-step approach starts with a 50g glucose challenge test, followed by a 100g OGTT if necessary, with similar diagnostic thresholds. [35].

This table consolidates the diagnostic criteria from WHO and ADA for DM, prediabetes and normal glucose levels, providing a clear comparison.

Condition	2-hour glucose	Fasting glucose	HbA1c
Diabetes Mellitus	WHO & ADA: ≥7.0 mmol/L (126 mg/dL)	WHO & ADA: ≥11.1 mmol/L (200 mg/dL)	WHO & ADA: ≥6.5% (48 mmol/mol)
Impaired fasting glycaemia	WHO: 6.1–6.9 mmol/L (110–125 mg/dL)	Not used for diagnosis	Not used for diagnosis
	ADA: 5.6–6.9 mmol/L (100–125 mg/dL)		
Impaired glucose tolerance	Not used for diagnosis	WHO & ADA: 7.8–11.0 mmol/L (140–199 mg/dL	Not used for diagnosis
GDM	1-step (WHO/ADA): 2-hour ≥8.5 mmol/L, 2-step ADA: 50g challenge followed by 100g OGTT	1-step approach ADA: FPG ≥5.1 mmol/L	Not used for diagnosis

Normal	WHO & ADA: <6.1 mmol/L (110 mg/dL)	WHO & ADA: <7.8 mmol/L (140 mg/dL)	WHO & ADA: <6.0% (42 mmol/mol) ADA: <6.0% (42 mmol/mol)

The WHO and ADA Diagnostic Guidelines for Diabetes [30].

DM: Diabetes Mellitus, HbA1c: Glycated Hemoglobin, DCCT: The Diabetes Control and Complications Trial, mmol/L: Millimoles per Liter, mg/dL: Milligrams per Deciliter.

Note: Reproduced from Glycaemic Control and Cognition: Evidence across the Lifespan, with permission from Taylor & Francis group

Type 1 Diabetes Mellitus (T1DM)

T1DM is a chronic condition that accounts for approximately 5% of diabetes cases and is characterized by insufficient insulin production due to the autoimmune destruction of pancreatic β-cells [36]. This autoimmune process is mediated by autoreactive T-cells that mistakenly target and destroy β-cells, which are crucial for insulin production and blood glucose regulation. The destruction of β-cells is often triggered by a combination of genetic susceptibility, such as variations in the HLA genes, and environmental factors, including viral infections and dietary components. This results in complete insulin deficiency [37,38].

T1DM is commonly known as juvenile or insulin-dependent diabetes because it primarily affects children and adolescents, although it can also occur in adults. In children, T1DM usually begins before the age of 15 [39]. However, a related condition called latent autoimmune diabetes in adults (LADA) can occur when the autoimmune process progresses more slowly, leading to the gradual destruction of β-cells and a later onset of symptoms [40].

The exact cause of T1DM remains unclear, but both environmental and genetic factors are believed to contribute. Environmental triggers such as viral infections (e.g. enteroviruses) and early dietary exposures (e.g. cow's milk) may initiate the autoimmune response [41,42]. Genetic predispositions, particularly variations in genes like HLA-DR and HLA-DQ, are associated with an increased risk of developing T1DM. As β-cell destruction progresses, significant insulin deficiency occurs, leading to hyperglycemia (high blood sugar) and ketosis [43,44]. If untreated, this can progress to diabetic ketoacidosis (DKA), a life-threatening condition characterized by severe dehydration, electrolyte imbalance and metabolic acidosis. Without timely insulin replacement therapy, DKA can result in coma or death [45,46].

Symptoms of T1DM often develop rapidly, usually within a few days to a week, and include polyuria (frequent urination), polydipsia (extreme thirst) and polyphagia (increased appetite). Other signs may include unexplained weight loss, fatigue, irritability, headaches and blurred vision [47,48]. T1DM is often diagnosed by detecting specific autoantibodies in the blood, such as glutamic acid decarboxylase antibodies (GAD), insulin autoantibodies (IAA) and islet cell antibodies (ICA). These are typically absent in T2DM [49]. Treatment for T1DM involves daily insulin injections or infusions via an insulin pump, along with careful monitoring, meal planning and regular physical activity [50]. Adhering to blood glucose targets, typically 80-130 mg/dL fasting and under 180 mg/dL postprandial according to ADA guidelines, is crucial for managing the condition effectively [51].

Type 2 Diabetes Mellitus (T2DM)

T2DM also known as Non-Insulin-Dependent Diabetes Mellitus (NIDDM), it is characterized by chronic hyperglycemia, insulin resistance, and a relative deficiency in insulin production [52]. It is the most prevalent form of diabetes, accounting for 90%-95% of cases. It predominantly affects middle-aged and older adults. This condition is associated with prolonged hyperglycemia due to poor lifestyle and dietary choices [53]. This multifactorial condition involves both genetic and environmental factors that impair β-cell function and reduce insulin sensitivity in muscle, liver, adipose tissue and the pancreas [54].

In T2DM, the body either fails to produce sufficient insulin or the cells become resistant to insulin [55]. Insulin resistance, often the earliest stage in the development of T2DM, occurs when cells become less responsive to insulin. Initially, this resistance impairs the body's ability to effectively use insulin, leading to elevated blood glucose levels. If left unaddressed, insulin resistance can progress to β-cell dysfunction, where the pancreas β-cells are damaged and produce inadequate insulin. As the demand for insulin increases, the pancreas ability to produce insulin gradually declines [56,57].

When glucose accumulates in the blood rather than entering cells, several complications can arise, including diabetic nephropathy (kidney damage), diabetic neuropathy (nerve damage), and an increased risk of cardiovascular diseases such as coronary artery disease [58]. T2DM is the leading cause of kidney failure, non-traumatic lower-limb amputations, and adult blindness in the United States [59].

The body initially compensates for insulin resistance by increasing insulin production to maintain normal blood glucose levels. However, factors such as obesity, physical inactivity, and chronic inflammation eventually result in IGT and

prolonged hyperglycemia, triggering inflammatory responses and oxidative stress. This leads to disruptions in glucose homeostasis and the secretion of factors like resistin from adipose tissue, which further exacerbates insulin resistance [60,61].

Symptoms of T2DM include polydipsia (increased thirst), polyuria (frequent urination), unintentional weight changes, polyphagia (persistent hunger), fatigue, blurred vision, delayed wound healing, recurrent infections, paraesthesia (tingling or numbness), acanthosis nigricans (darkened skin patches), impaired immune function, and hypertension (high blood pressure) [62].

Managing T2DM requires a combination of pharmacological therapy, dietary modifications, and regular physical activity to mitigate complications such as cardiovascular disease, neuropathy, nephropathy (kidney disease), retinopathy, dermatological conditions, impaired wound healing, hearing loss, sleep apnea and cognitive decline, including dementia [63]. Oral diabetes medications, such as metformin, are commonly prescribed to reduce hepatic glucose production and manage blood glucose levels [64]

Gestational Diabetes Mellitus (GDM)

GDM occurs during pregnancy and is considered a precursor to future T2DM. It is characterized by glucose intolerance that first emerges during pregnancy [65]. Pregnancy is a diabetogenic state due to increased insulin resistance caused by placental hormones, including human placental lactogen, estrogen and progesterone. These hormones are essential for ensuring an adequate glucose supply for the growing fetus but can lead to elevated blood glucose levels in some women, resulting in GDM [66].

If left unmanaged, GDM can pose significant risks to both the mother and the fetus. For the fetus, complications may include macrosomia (large birth weight), congenital malformations such as sacral agenesis, and an increased risk of stillbirth. For the mother, unmanaged GDM can lead to preeclampsia, a higher likelihood of cesarean delivery and an increased risk of developing T2DM later in life [67,68].

GDM typically develops in the second trimester and is marked by elevated blood glucose levels, which, if left unmanaged, can lead to complications similar to, but generally less severe than, those seen in other forms of diabetes [69]. The condition is linked to decreased pancreatic β-cell function, increased insulin resistance during pregnancy, and hormonal changes. Factors like genetic predisposition, obesity and placental hormones contribute to hyperglycemia in women predisposed to GDM. Risk factors for GDM include genetic predisposition, obesity, advanced maternal age, a history of GDM in previous pregnancies and belonging to ethnic groups with a high prevalence of T2DM, such as Hispanic, African American, Native American or Asian American descent. Polycystic Ovary Syndrome (PCOS), characterized by irregular menstrual periods, elevated androgen levels and persistent symptoms like glucosuria, acne and hirsutism, is also linked to GDM. During pregnancy, hormones produced by the placenta can affect the body's ability to use insulin effectively, leading to glucose accumulation in the blood [70,71].

Unlike T1DM, which can be triggered by hormonal produced during pregnancy that affect insulin effectiveness, GDM is often linked to factors such as high blood pressure, obesity, a family history of diabetes and PCOS. Insulin resistance in GDM is caused by excess fat and hormonal imbalances, leading to decreased insulin sensitivity. Obesity and high blood pressure promote inflammation, while PCOS impairs glucose regulation. A family history of diabetes and a previous history of GDM indicate genetic predisposition and cumulative impact on insulin sensitivity, increasing the risk of developing GDM [72,73]

Diagnosis of GDM is typically made between 24 and 28 weeks of pregnancy using a glucose tolerance test. [74]. Unmanaged GDM can lead to complications for both the mother and the child, including preeclampsia, cesarean delivery and an increased risk of future T2DM. The baby may face issues such as macrosomia, hypoglycemia, jaundice, respiratory distress and an increased risk of stillbirth, neonatal seizures and developmental delays. Both mother and child may also experience long-term health issues related to metabolic disorders [75].

Management of GDM usually involves dietary changes and regular physical activity. In some cases, medication or insulin injections may be required to stabilize blood glucose levels, with insulin being commonly used for control. Oral medications such as metformin and glyburide may also be prescribed, although insulin is preferred if these oral agents are ineffective or if there are concerns about fetal safety [76,77].

Feature	T1DM	T2DM	GDM	Prediabetes
Prevalence	5% of diabetes cases	90%-95% of diabetes cases	14%Occurs during pregnancy	9.1%. prediabetes cases

Onset	Typically in children or adolescents	Typically in adults, but increasingly in younger individuals	Develops during pregnancy	Can develop into T2DM
Insulin Production	No insulin production due to loss of pancreatic β-cells	Insufficient insulin production and insulin resistance	Insulin resistance during pregnancy	Normal insulin production but insulin resistance
Insulin Resistance	Generally low; insulin is absent	High; cells do not respond properly to insulin	Increased due to placental hormones affecting insulin action	Elevated insulin resistance
Symptoms	Frequent urination, excessive thirst, weight loss, fatigue	Similar to T1DM, but also includes blurred vision, slow healing wounds	Similar to T1DM and T2DM, may also include high blood pressure	Elevated blood glucose, but not yet diabetic
Complications	Diabetic retinopathy, nephropathy, neuropathy, cardiovascular diseases	Same as T1DM, with higher risk of cardiovascular diseases	Macrosomia, hypoglycemia, jaundice, respiratory distress	Increased risk of developing T2DM, heart disease
Management	Insulin injections or pump, monitoring blood glucose levels	Lifestyle changes (diet, exercise), oral medications, insulin if needed	Dietary changes, physical activity, insulin if necessary	Lifestyle changes to prevent progression to T2DM
Long-term Risk	High risk of long-term complications without management	High risk of long-term complications if poorly managed	Risk of developing T2DM later in life	Higher risk of T2DM

Table 2: Comparison of Diabetes Types and Prediabetes [36 to 77]

Maturity Onset Diabetes of the Young (MODY):

MODY is a subtype of non-insulin-dependent diabetes mellitus (NIDDM), characterized by an early onset, typically before 25 years of age, and an autosomal dominant inheritance pattern [78]. First recognized by Tattersall in 1974, MODY results from mutations in specific genes that impair β-cell function and insulin production. Although MODY accounts for only 1% of diabetes cases, it is frequently misdiagnosed as T1DM or T2DM due to overlapping clinical features [79]. Unlike these more common forms, MODY is non-ketotic, and patients lack pancreatic autoantibodies. MODY can be diagnosed using genetic testing, which has identifying mutations in at least 14 genes, with the most common mutations occurring in glucokinase (GCK), hepatocyte nuclear factor-1 alpha (HNF1A), and hepatocyte nuclear factor-4 alpha (HNF4A) [80].

MODY 1 is associated with mutations in the HNF4A gene, leading to progressive β-cell dysfunction and an increased risk of microvascular complications like retinopathy and nephropathy. Sulfonylureas which stimulate insulin secretion, are

typically effective in managing this subtype, delaying the need for insulin therapy.[79]

MODY 2 is caused by mutations in the GCK gene, affecting glucose sensing in β-cells. It leads to mild, stable hyperglycemia, which is generally managed through lifestyle interventions such as diet and exercise. Oral hypoglycaemic agents like sulfonylureas and metformin are ineffective for this subtype, as clinical trials have shown they have minimal impact on glycemic control.[81]

MODY 3 the most common subtype, is caused by mutations in the HNF1A gene. It often presents with insulin resistance and a higher risk of microvascular complications. Similar to MODY 1, sulfonylureas are effective in enhancing insulin secretion and improving glycemic control in patients with MODY 3.[82]

MODY 4 results from mutations in the PDX1 gene, which plays a role in pancreatic development. This subtype often involves more severe β-cell dysfunction, requiring intensive management due to a higher risk of complications related to blood glucose control [83].

MODY 5 is linked to mutations in the HNF1B gene and frequently presents with renal abnormalities such as cysts and potential renal impairment. These extra-pancreatic manifestations are a notable feature of this subtype, with management focusing on both renal and glycemic issues.[84]

MODY 6 arises from mutations in the NEUROD1 gene, which is involved in pancreatic β-cell development. It is a less common subtype, with variable presentation and complications related to glucose regulation.[85]

MODY 7-13 includes subtypes caused by mutations in various other genes such as KLF11, PAX4 and CEL, each with different effects on β-cell function and insulin production. Management and complications vary depending on the specific gene involved.[86]

Latent Autoimmune Diabetes in Adults (LADA)

LADA is typically defined as diabetes diagnosed after the age of 35 and presents with features of both T1DM and T2DM [87]. Often referred to as Type 1.5 diabetes, LADA shares characteristics with both forms, distinguishing LADA from T1DM and T2DM can be challenging due to similarities in pathogenesis and clinical manifestations [88,89]. Similar to T1DM, LADA is associated with the presence of autoantibodies, indicating an autoimmune origin where the immune system mistakenly targets and destroys insulin-producing beta cells within the pancreas However, this autoimmune process in LADA tends to progress more slowly than in classic T1DM [90]. Early diagnosis is crucial to slow disease progression. Diagnostic biomarkers for LADA include autoantibodies against beta cells and C-peptide levels [82]. LADA is considered by a slower destruction of beta cells compared to T1DM due to a less aggressive autoimmune response while retaining some metabolic features of T2DM, such as insulin resistance. [91]. Key autoantibodies associated with LADA include Glutamic Acid Decarboxylase Autoantibodies (GADA), Islet Cell Autoantibodies (ICA), Insulinoma-Associated Autoantibodies (IA-2) and Zinc Transporter Autoantibodies (ZnT8); GADA is particularly common in cases of T1DM [92]. The diagnostic criteria for Latent Autoimmune Diabetes in Adults (LADA) include: (1) adult onset of diabetes; (2) initial insulin independence; and (3) the presence of circulating islet autoantibodies, such as anti-GAD, anti-IA-2 and anti-insulin autoantibodies. While criteria (1) and (2) are also observed in T2DM, criterion (3) the presence of islet autoantibodies serves as a distinguishing feature of LADA. These autoantibodies are detected through blood tests using techniques such as enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), or electrochemiluminescence immunoassay (ECLIA). These methods help identify autoimmune activity targeting pancreatic beta cells, a characteristic typically absent in T2DM. Consequently, the detection of islet autoantibodies plays a critical role in differentiating LADA from T2DM [93].

Maternally Inherited Diabetes and Deafness (MIDD)

MIDD is a rare type of diabetes caused by mutations in mitochondrial DNA, such as those in the MT-TL1, MT-TK or MT-TE genes, representing 1% to 2% of diabetes cases. It is characterized by its occurrence in individuals with mitochondrial genetic mutations and can be present in patients with diabetes, but not exclusively limited to those already diagnosed with the condition [94]. The primary features of MIDD include diabetes and hearing loss, both of which are inherited in a maternal pattern due to mutations in mitochondrial DNA. This inheritance pattern occurs because mitochondrial DNA is passed down exclusively from the mother [95]. The mutation leads to a drop in the functional capacity of mitochondrial respiratory enzyme complexes, particularly Complex I (NADH oxidoreductase) and Complex IV (cytochrome c oxidase), resulting in decreased ATP production. This impaired ATP generation in pancreatic beta cells causes insulin deficiency, which ultimately leads to diabetes [96, 97]. The most common mutation linked to MIDD is an A to G transition at position 3243 (m.3243A > G) in the *MT-TL1* gene, which encodes mitochondrial tRNA for leucine. This mutation disrupts mitochondrial protein synthesis, disrupting the electron transport chain, especially Complex I and IV. As a result, pancreatic beta cells, which are highly reliant on efficient ATP production for insulin secretion, become dysfunctional, leading to the onset of diabetes [98]. MIDD is often associated with macular dystrophy and sensorineural hearing loss, particularly affecting high-frequency tones, caused by damage to the auditory nerve or inner ear [99]. The diagnosis of MIDD typically involves genetic testing to identify

specific mitochondrial DNA mutations, which is crucial for confirming the condition and distinguishing it from other forms of diabetes Additionally, audiometry or other forms of hearing testing are often used to detect the sensorineural hearing loss commonly associated with MIDD. The typical age of onset for MIDD is in early adulthood, though symptoms can appear earlier depending on the severity of the mitochondrial mutation [100, 101].

Neonatal Diabetes Mellitus (NDM)

NDM is a rare form of diabetes, occurring in approximately 0.0002% to 0.00025% of live births. It typically presents within the first six months of life and persists for at least two weeks, differentiating it from transient neonatal hyperglycemia, which can occur briefly due to non-genetic factors and resolves without long-term effects [102]. Unlike more common forms of diabetes such as Type 1, Type 2, or MODY, NDM is caused primarily by genetic mutations that affect insulin production or regulation early in life [103]. Several genes, including KCNJ11, ABCC8, INS, GCK, PDX1, EIF2AK3 and FOXP3 are implicated in NDM, impacting insulin secretion, glucose sensing and pancreatic beta-cell development [104]. For example, mutations in KCNJ11 and ABCC8 disrupt the function of ATP-sensitive potassium (KATP) channels, impairing insulin release, while mutations in GCK affect glucose sensing in beta cells. Mutations in EIF2AK3 can cause Wolcott-Rallison syndrome, a condition characterized by neonatal diabetes, skeletal dysplasia, growth retardation, liver dysfunction and developmental delay [105,106].NDM can be classified into two main subtypes: Transient Neonatal Diabetes Mellitus (TNDM) and Permanent Neonatal Diabetes Mellitus (PNDM). TNDM is a temporary condition that typically resolves within a few months and is often caused by overexpression of chromosome 6q24, although some individuals may experience a recurrence of diabetes later in life [107,108]. In contrast, PNDM is a lifelong condition, most often resulting from mutations in the KATP channel genes, particularly KCNJ11 and ABCC8 [109]. The pathophysiology of NDM involves abnormal pancreatic development, beta-cell dysfunction or accelerated beta-cell loss, leading to insulin deficiency and hyperglycemia[110]. While genetic mutations are the primary cause of NDM, secondary factors such as environmental influences or maternal conditions (e.g., GDM) can also play a role in some cases [111].

Management of Diabetes

A diabetes diet is a structured nutritional plan aimed at controlling blood glucose levels through the intake of fruits, vegetables, lean proteins and whole grains, while reducing saturated fats, refined carbohydrates and sugars. Carbohydrate counting, particularly essential for individuals with T1DM or those on insulin therapy, helps regulate insulin administration. A registered dietitian can develop personalized meal plans tailored to health goals, preferences and lifestyle [112].

Physical activity is essential for all individuals, including those with diabetes, as it helps lower blood glucose by facilitating the uptake of glucose into cells for energy and increasing insulin sensitivity. It is important to obtain medical approval before starting any exercise regimen and to select enjoyable activities to maintain consistency. The goal is at least 30 minutes of moderate physical activity most days, or a total of 150 minutes per week. Begin gradually and avoid sitting for more than 30 minutes [113].

To maintain a healthy weight, consult the healthcare team regarding strategies such as calorie reduction, increased physical activity, or the use of medications or surgery. Adequate sleep, typically 7 to 8 hours for adults, improves mood, energy and blood glucose levels, with children and adolescents requiring more. Mental health management is essential, as stress, sadness or anger can impact individuals with chronic illnesses like diabetes. Reducing stress and seeking support from healthcare or mental health professionals is recommended [114].

Pharmacological Treatment of Diabetes

A. Oral Medications

1. Biguanides:

Biguanides such as Metformin is the first-line treatment for managing T2DM. It primarily works by reducing hepatic glucose production and enhancing insulin sensitivity, which helps lower blood glucose levels without increasing insulin secretion, making it a safe and widely-used option. Metformin, limit the liver's glucose release and improve the body's response to insulin. They are effective and low-cost, with potential benefits like minor weight loss. However, side effects can include nausea, stomach pain, diarrhea and in rare cases, lactic acidosis, especially in patients with kidney or liver dysfunction.

2. Sulfonylureas:

These medications stimulate the pancreas to increase insulin secretion, which helps lower blood glucose levels. However, they carry a risk of hypoglycemia because insulin is produced regardless of current blood glucose levels. Sulfonylureas, such as Glipizide, Glimepiride and Glyburide, are cost-effective options for improving blood glucose control by promoting insulin release from the pancreas. Despite their effectiveness, they can have negative effects such as weight gain, hypoglycaemia and, in rare instances, allergic reactions like skin rashes [114].

3. **Dipeptidyl peptidase-4 (DPP-4)** Inhibitors:

These medications work by inhibiting the enzyme **DPP-4**, leading to increased levels of **incretin hormones**. Incretins stimulate insulin release from the pancreas and decrease the production of **glucagon**, a hormone that raises blood sugar levels, thereby improving glucose regulation after meals. **DPP-4 inhibitors**, such as **Saxagliptin (Onglyza)**, **Sitagliptin (Januvia)**, **Linagliptin (Tradjenta)** and **Alogliptin (Nesina)**, promote insulin secretion in response to rising blood glucose levels while limiting hepatic glucose release. These medications do not typically cause weight gain or hypoglycemia, but they may be associated with some side effects such as nausea, sore throat, cough, headache and allergic reactions such as skin rash.

4. Sodium-glucose co-transporter 2 (SGLT2) Inhibitors:

SGLT2 inhibitors function by inhibiting glucose reabsorption in the renal proximal tubules, thereby increasing glucosuria and reducing plasma glucose levels. In addition to their hypoglycaemic effects, SGLT2 inhibitors confer cardiovascular benefits, such as a reduction in the risk of heart failure and progression of renal impairment. Examples of SGLT2 inhibitors include Canagliflozin (Invokana), Dapagliflozin (Farxiga), Empagliflozin (Jardiance) and Ertugliflozin (Steglatro).These agents enhance urinary glucose excretion, which may lead to modest weight loss and reductions in blood pressure. However, they are associated with an increased risk of genitourinary infections, including urinary tract infections and genital mycotic infections.

5. Thiazolidinediones (TZDs):

TZDs are PPAR-γ (peroxisome proliferator-activated receptor) agonists that increase insulin sensitivity in the liver, skeletal muscle and adipose tissue. Examples of these TZDs include pioglitazone and rosiglitazone. These agents enhance cellular response to insulin, thereby promoting glucose uptake and reducing hepatic gluconeogenesis. The use of TZDs is linked to negative effects like weight gain, fluid retention, an increased risk of bone fractures and the possibility of cardiovascular problems, including heart failure, even though they may only slightly raise high-density lipoprotein (HDL) cholesterol. Long-term use is also associated with an increased risk of bladder cancer. As a result, people with a history of heart failure or liver disease should not take TZDs [115].

B. Insulin Therapy

Insulin therapy is essential for managing T1DM, where the body does not produce insulin and it is also used in advanced cases of T2DM when oral medications are insufficient.

Types of Insulin:

Short-acting (regular) insulin: Short-acting insulin, also known as regular insulin, is commonly used to manage postprandial blood glucose spikes. It begins to take effect within 30 to 60 minutes before a meal, with a duration of action lasting between 3 to 8 hours. Injection into the abdominal region is recommended for better absorption and effectiveness.

Intermediate acting insulin: Intermediate-acting insulin, such as NPH insulin, provides basal insulin coverage for 12 to 18 hours and is commonly used in conjunction with rapid- or short-acting insulin to manage both fasting and postprandial blood glucose levels. It is often administered up to 1 hour prior to a meal to help maintain stable blood glucose levels throughout the day and overnight.

Long acting insulin: Long-acting insulin, such as insulin glargine or insulin detemir, provides a consistent and prolonged insulin release over a 24-hour period, assisting in the maintenance of baseline glucose control. It is commonly used to manage fasting glucose levels and is frequently combined with rapid- or short-acting insulin to cover postprandial glucose spikes for total glycemic control.

Rapid acting insulin: Rapid-acting insulin, such as insulin lispro, aspart or glulisine, is administered about 15 minutes before meals to provide quick control of postprandial blood glucose spikes. It begins working within minutes and lasts for 1 to 5 hours. Rapid-acting insulin is often paired with a long-acting insulin to maintain overall glycaemic control throughout the day.

Premixed: Premixed insulin formulations, such as Humulin and Novolog, combine short-acting or rapid-acting insulin with intermediate-acting insulin in a single vial or insulin pen for simplified administration. These combinations provide both basal and prandial insulin coverage, offering convenience for patients. The timing of administration depends on the specific product, with some requiring injection 10 minutes before meals, while others should be administered 30 to 45 minutes prior to eating [116].

Insulin Taking MethodsShots or Pens: Inject insulin into the adipose tissue below the skin using a syringe and needle. The frequency and dosage of insulin injections vary based on the type of diabetes, individual blood glucose levels, and daily activities, ensuring appropriate glycemic control tailored to each patient's needs.

An insulin pump is a device that delivers small, steady amounts of rapid-acting insulin throughout the day. It can deliver an immediate spike in insulin when taken with meals.

Inhaled insulin, such as Afrezza is taken at the beginning of each meal through an inhaler. It's not recommended for smokers or those with lung conditions due to potential respiratory issues [117].

The basal-bolus regimen combines long-acting insulin (to meet baseline insulin requirements) with short-acting insulin before meals to mimic the body's natural insulin release patter. The body requires a constant supply of insulin throughout the day and night, even between meals. This is known as 'basal' insulin. It regulates your blood sugar levels when you're not eating but your body still requires energy. Basal insulin is typically injected once a day at bedtime, but it may be necessary to inject twice a day in some people because it does not last 24 hours. Bolus insulin, taken before meals, includes ultra-fast-acting options like Fiasp, rapid-acting analogues like NovoRapid, Humalog or Apidra and short-acting insulins such as Insuman Rapid or Humulin S. Together, this regimen provides comprehensive glucose control throughout the day [118].

C. Newer Medications

GLP-1 Receptor Agonists: Liraglutide is an example of a GLP-1 receptor agonist, which mimics the actions of the incretin hormone GLP-1. In the end, this improves blood sugar control by increasing insulin secretion in response to food intake, decreasing glucagon release and delaying stomach emptying. These medications also encourage weight loss, which is beneficial for many people with T2DM [119].

Combination Therapies: Multiple drugs are used together to improve glucose control. for example, Metformin is frequently coupled with other kinds of medications, such as SGLT2 inhibitors or GLP-1 receptor agonists, to target different elements of diabetes care, such as boosting insulin sensitivity, increasing insulin production, and efficiently decreasing blood sugar levels [120].

Current Research and Advances in Diabetes

Gene Therapy: The goal of gene therapy for diabetes is to fix the genetic defects that cause Type 1 and some types of monogenic diabetes (like MODY). By changing or adding functional genes, the intention is to either improve insulin sensitivity or restore normal insulin production. Promising studies are investigating the application of CRISPR-Cas9 technology to target autoimmunity or fix insulin gene mutations in T1DM, which may result in a cure or long-term remission.

Immunotherapy: T1DM is a disease where insulin-producing beta cells in the pancreas are mistakenly attacked and destroyed by the immune system; immunotherapy tries to modulate or retrain the immune system to stop further damage to these cells.Treatments such as T-cell modulation and antigen-based vaccines are being investigated in ongoing clinical trials. These treatments are designed to target specific immune cells (T-cells) involved in the autoimmune response, or to introduce antigens that help the immune system recognize beta cells as harmless. The goal is to slow down or stop the destruction of beta cells, potentially stopping the progression of T1DM, especially if administered early in the disease.

Stem cell therapy: Stem cell therapy in diabetes focuses on creating insulin-producing cells, such as beta cells, from stem cells to replace the damaged or destroyed pancreatic cells in T1DM. Since T1DM occurs when the body's immune system attacks and destroys its own beta cells, stem cell therapy offers a potential way to regenerate these cells [121].

Diabetes Technology

Artificial Pancreas Systems: These systems combine insulin pumps and continuous glucose monitoring (CGM) equipment to automatically modify insulin dosage in response to current glucose readings. The direction of technological advancements is toward completely automated closed-loop systems, sometimes referred to as "artificial pancreas," that require minimal way of human intervention [122].

Continuous Glucose Monitors (CGMs): CGMs provide real-time blood glucose data, allowing for more precise and dynamic glucose management. These devices are made up of a small sensor that is placed under the skin and continuously measures glucose levels before sending the information to a receiver or a compatible device. Recent advancements have improved accuracy, durability and usability, making CGMs more dependable and user-friendly. Some modern CGMs now integrate with smartphones and smartwatches, allowing users to track their glucose levels in real time and receive alerts for high or low blood sugar, thereby improving diabetes convenience and proactive management [123].

Insulin Delivery Systems: Insulin delivery systems are developing, with next-generation insulin pumps that are smaller, more programmable, and wirelessly connected, enabling better convenience and flexibility for diabetes management. Research is also being conducted on smart insulin, which would activate automatically in response to growing blood glucose levels. This "self-regulating" insulin eliminates the need for frequent dose modifications, making management easier and providing patients with more stable glucose control [117].

2. CONCLUSION

Diabetes mellitus (DM) represents a growing global health challenge, influenced by a complex interplay of genetic,

environmental, and lifestyle factors. This review has provided a comprehensive overview of the classification, pathophysiology, and management techniques for various forms of diabetes, including Type 1, Type 2, gestational diabetes, and rarer variants such as MODY and LADA. Early diagnosis and individualized, comprehensive treatment techniques are still crucial for avoiding problems and enhancing long-term outcomes.

Advances in pharmacological treatments, such as newer classes of oral medications, injectables like GLP-1 receptor agonists, and cutting-edge technologies like continuous glucose monitoring and artificial pancreas systems, offer promising solutions for better disease management. However, challenges such as disease progression, complications, treatment adherence, and disparities in healthcare access continue to hinder effective management.

Looking ahead, continued research into emerging therapies, such as gene therapy, immunotherapy, and stem cell treatments, is essential to overcoming these challenges and advancing diabetes care. The worldwide burden of diabetes underscores the urgent need for coordinated public health efforts and innovative treatment strategies to reduce the incidence and improve the quality of life for those affected. Collaboration across healthcare systems, research institutions, and governments will be critical in achieving these goals

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