Diabetes Mellitus: From Pathophysiology to Novel Therapeutic Strategies-A Comprehensive Review

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Abstract
Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycaemia resulting from impaired insulin secretion, insulin resistance, or a combination of both. It represents a major global public health challenge because of its increasing prevalence and its association with substantial morbidity, mortality, and healthcare burden. Diabetes mellitus comprises several distinct forms, including type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and specific forms such as latent autoimmune diabetes in adults (LADA), maturity-onset diabetes of the young (MODY), and neonatal diabetes mellitus. Prediabetes represents an intermediate state of dysglycaemia and is an important risk factor for the development of T2DM. The pathogenesis of diabetes is multifactorial and involves genetic susceptibility, autoimmune mechanisms, insulin resistance, pancreatic β-cell dysfunction, obesity, environmental influences, and metabolic abnormalities. Persistent hyperglycaemia can result in acute complications, including hypoglycaemia, diabetic ketoacidosis, and hyperosmolar hyperglycaemic state, as well as chronic microvascular and macrovascular complications affecting the kidneys, eyes, nervous system, cardiovascular system, and peripheral vasculature. Early diagnosis using fasting plasma glucose, oral glucose tolerance testing, glycated haemoglobin, and appropriate clinical assessment is essential for timely intervention. Management involves individualized lifestyle modification, nutritional therapy, physical activity, glucose-lowering pharmacotherapy, and insulin therapy when indicated. Recent advances have expanded the therapeutic landscape through incretin-based therapies, dual GIP/GLP-1 receptor agonists, SGLT2 inhibitors with cardiorenal benefits, novel insulin formulations, immunotherapy for T1DM, stem-cell-derived β-cell replacement, continuous glucose monitoring, automated insulin delivery, and digital health technologies. Current approaches increasingly emphasize patient-centred and personalized treatment, with therapeutic selection guided not only by glycaemic control but also by cardiovascular, renal, metabolic, and quality-of-life considerations. Continued research into disease-modifying therapies, β-cell preservation, cellular replacement, precision medicine, and artificial intelligence may further transform diabetes prevention and management.

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Introduction

Diabetes mellitus (DM) is a chronic, progressive metabolic disorder characterized by persistent hyperglycaemia resulting from inadequate insulin secretion, impaired insulin action, or a combination of both. It is one of the most common metabolic and endocrine disorders worldwide and represents a major public health challenge because of its increasing prevalence, associated

morbidity and mortality, and substantial economic burden. [1] Diabetes mellitus is broadly classified into type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM). Type 1 diabetes is primarily an autoimmune disorder characterized by destruction of pancreatic β-cells, resulting in an absolute deficiency of insulin. Type 2 diabetes is the most common form of diabetes and is characterized by varying degrees of insulin resistance, progressive impairment of pancreatic β-cell function, and inadequate insulin secretion. It is associated with several risk factors, including obesity, unhealthy dietary habits, physical inactivity, and genetic predisposition. Gestational diabetes mellitus refers to diabetes diagnosed during pregnancy and is associated with an increased risk of adverse maternal and fetal outcomes, as well as an increased risk of developing type 2 diabetes in the future. [2]

Accurate classification of diabetes is important because it helps determine the underlying cause of hyperglycaemia and guides appropriate therapeutic management. The traditional classification based solely on age at diagnosis is no longer considered reliable. Although type 1 diabetes is commonly diagnosed in children and young adults and type 2 diabetes is more common in adults, either type can occur at any age. Therefore, diabetes should be classified according to its underlying pathophysiological mechanism rather than age alone. [3]

Persistent hyperglycaemia can progressively damage multiple organs and tissues, particularly the blood vessels, eyes, kidneys, heart, and nervous system. Diabetes is therefore associated with both microvascular and macrovascular complications, including diabetic retinopathy, nephropathy, neuropathy, cardiovascular disease, stroke, peripheral vascular disease, and lower-limb amputation. The common clinical manifestations of diabetes include polyuria, polydipsia, unexplained weight loss, polyphagia, fatigue, and blurred vision. [4] Early diagnosis, appropriate lifestyle modification, regular monitoring, and individualized pharmacological therapy are essential for achieving adequate glycaemic control, preventing or delaying diabetes-related complications, and improving the quality of life of individuals with diabetes.

The global prevalence of diabetes has increased substantially over the past few decades, with the greatest increase occurring in low- and middle-income countries. The growing prevalence of type 2 diabetes is driven by population ageing, urbanization, increasing obesity, unhealthy dietary patterns, and physical inactivity. The disease is no longer restricted to older adults, and an increasing number of younger individuals are being diagnosed with type 2 diabetes. [5] Diabetes in older adults is also becoming increasingly prevalent and is frequently associated with multiple comorbidities. Some of these conditions may arise as a consequence of the progression of diabetes, whereas others may occur independently but contribute to increased disease burden and therapeutic complexity. [6]

Historically, it was estimated that approximately 285 million adults worldwide were living with diabetes in 2010, corresponding to about 6.6% of the adult population, and this number was projected to increase to approximately 438 million by 2030. [5] These earlier projections highlight the rapid growth of the global diabetes epidemic; however, more recent estimates indicate that the actual burden has increased beyond these projections. India is among the countries with the largest number of people living with diabetes and has experienced a substantial increase in the prevalence of both diagnosed and undiagnosed diabetes. The high burden of diabetes in India has been attributed to a combination of genetic susceptibility and environmental and lifestyle factors. The characteristic Asian Indian phenotype includes increased insulin resistance and a greater tendency toward abdominal adiposity, even at comparatively lower body mass indices. In addition, rapid urbanization, unhealthy dietary practices, reduced physical activity, and increasing obesity have contributed significantly to the growing burden of type 2 diabetes in the Indian population.

Types of Diabetes Mellitus

Diabetes mellitus can be classified into several forms based on its underlying pathophysiology, genetic factors, and clinical characteristics. The major forms include type 1 diabetes mellitus, type 2 diabetes mellitus, and gestational diabetes mellitus. In addition, several specific forms of diabetes, including monogenic diabetes, latent autoimmune diabetes in adults, neonatal diabetes, and other secondary forms, may occur.

1. Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is primarily an autoimmune disorder characterized by the destruction of pancreatic β-cells, resulting in an absolute deficiency of insulin. It commonly develops during childhood or adolescence but can occur at any age. Individuals with type 1 diabetes generally require lifelong insulin therapy for survival. Type 1 diabetes accounts for approximately 5–10% of all diabetes cases, although its prevalence varies among populations.

2. Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes, accounting for the majority of diabetes cases worldwide. It is characterized by insulin resistance, progressive decline in pancreatic β-cell function, and inadequate insulin secretion relative to the body's requirements. Type 2 diabetes is strongly associated with obesity, abdominal adiposity, physical inactivity, unhealthy dietary patterns, increasing age, and genetic susceptibility. Although it is more common in adults, it can also occur in children, adolescents, and young adults, particularly in association with obesity and other metabolic risk factors.

3. Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is defined as diabetes diagnosed during pregnancy that was not clearly present before pregnancy. It develops primarily as a result of increased insulin resistance associated with pregnancy, particularly during the second and third trimesters. Gestational diabetes may resolve after delivery; however, women with a history of GDM have an increased risk of developing type 2 diabetes mellitus and recurrent gestational diabetes in subsequent pregnancies. GDM is also associated with an increased risk of adverse maternal and fetal outcomes.

4. Prediabetes

Prediabetes is not a type of diabetes mellitus, but rather an intermediate metabolic state in which blood glucose levels are higher than normal but do not meet the diagnostic criteria for diabetes. It includes impaired fasting glucose and/or impaired glucose tolerance and is associated with an

increased risk of progression to type 2 diabetes mellitus. Prediabetes is also associated with an increased risk of cardiovascular and other metabolic complications.

5. Latent Autoimmune Diabetes in Adults

Latent autoimmune diabetes in adults (LADA) is a slowly progressive form of autoimmune diabetes that develops during adulthood. Individuals with LADA have evidence of pancreatic β-cell autoimmunity and initially may not require insulin therapy. Because β-cell function progressively declines, insulin therapy may eventually become necessary. LADA may initially be misdiagnosed as type 2 diabetes because of its adult onset and relatively slow progression. Although it is commonly diagnosed after 30 years of age, age alone is not sufficient to define LADA.

6. Maturity-Onset Diabetes of the Young

Maturity-onset diabetes of the young (MODY) is a group of monogenic forms of diabetes caused by pathogenic variants in a single gene involved in pancreatic β-cell development, function, or insulin secretion. MODY typically has an early age of onset, often before 25 years, and is usually inherited in an autosomal dominant pattern. Unlike the common forms of diabetes, MODY is not primarily caused by autoimmune β-cell destruction or typical insulin resistance. Genetic testing is important for confirming the diagnosis and guiding appropriate treatment.

7. Neonatal Diabetes Mellitus

Neonatal diabetes mellitus (NDM) is a rare form of monogenic diabetes that develops during the first six months of life. It results from genetic abnormalities affecting pancreatic β-cell development, insulin production, or insulin secretion. Neonatal diabetes may be transient or permanent, depending on the underlying genetic cause. Identification of the genetic defect is important because some forms can be effectively treated with specific oral antidiabetic therapy rather than lifelong insulin therapy.

8. Brittle Diabetes Mellitus

Brittle diabetes, also referred to as labile diabetes, is a rare and severe form of diabetes characterized by frequent, unpredictable, and difficult-to-control fluctuations in blood glucose levels, with recurrent episodes of severe hypoglycaemia and hyperglycaemia. It is most commonly associated with advanced or difficult-to-manage type 1 diabetes and may be influenced by factors such as impaired glucose counter-regulation, psychological factors, irregular food intake, malabsorption, or other underlying medical conditions. Management requires intensive individualized diabetes care, including optimization of insulin therapy, continuous glucose monitoring, dietary management, and treatment of contributing factors. In highly selected patients with severe, refractory disease, pancreas or pancreatic islet transplantation may be considered; however, transplantation is not routinely required and carries significant risks.

Type 1 Diabetes Mellitus (T1dm)

Type 1 diabetes mellitus (T1DM), also referred to as type 1A diabetes mellitus, was previously known as insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes. It accounts for approximately 5–10% of all cases of diabetes mellitus. T1DM is primarily an autoimmune disorder characterized by immune-mediated destruction of insulin-producing pancreatic β-cells, predominantly involving autoreactive T lymphocytes. Progressive destruction of pancreatic β-cells results in an absolute deficiency of insulin, leading to persistent hyperglycaemia. T1DM can develop at any age and affects both children and adults. Individuals with established T1DM require lifelong exogenous insulin therapy to maintain glycaemic control and prevent life-threatening metabolic complications. [7-9]

The exact aetiology of T1DM remains incompletely understood; however, the disease is believed to result from a complex interaction between genetic susceptibility and environmental factors. Among the genetic determinants, the human leukocyte antigen (HLA) class II region, particularly the HLA-DR3 and HLA-DR4 haplotypes, is strongly associated with susceptibility to T1DM. In addition to HLA-associated susceptibility, several non-HLA genes involved in immune regulation, insulin synthesis, and pancreatic β-cell function have also been implicated in disease development. Environmental factors are thought to contribute to the initiation or progression of β-cell autoimmunity, although the specific factors and mechanisms remain incompletely defined. The importance of environmental influences is supported by observations such as incomplete concordance of T1DM among genetically identical twins, indicating that genetic susceptibility alone is insufficient to explain disease development. [10]

The autoimmune destruction of pancreatic β-cells is associated with the development of islet autoantibodies, which serve as important biomarkers of β-cell autoimmunity and disease risk. Major autoantibodies associated with T1DM include glutamic acid decarboxylase 65 (GAD65) antibodies, insulin autoantibodies (IAA), islet cell antibodies (ICA), insulinoma-associated antigen-2 (IA-2) antibodies, and zinc transporter 8 (ZnT8) antibodies. The presence of multiple islet autoantibodies is associated with a substantially increased risk of progression to clinical T1DM. [11]

The rate of progression of T1DM varies considerably among individuals and is influenced by factors such as age, genetic background, and the degree of autoimmune β-cell destruction. In children and adolescents, β-cell destruction may progress relatively rapidly, resulting in an abrupt onset of severe insulin deficiency. Consequently, some patients initially present with diabetic ketoacidosis (DKA), particularly when the disease remains undiagnosed. In other individuals, β-cell destruction may progress more gradually, resulting in a period of mild or moderate hyperglycaemia before the development of overt insulin deficiency. During physiological stress, such as severe infection, the increased metabolic demand for insulin may precipitate marked hyperglycaemia or DKA in individuals with substantial β-cell loss.

In adults, the decline in β-cell function may occur more slowly, and residual endogenous insulin secretion can persist for several years after diagnosis. This residual β-cell function may initially reduce the risk of DKA and maintain partial glycaemic control. However, progressive loss of β-cell function ultimately results in severe insulin deficiency, increasing hyperglycaemia, and reduced endogenous insulin secretion. Plasma C-peptide concentrations may become very low or undetectable, reflecting markedly reduced endogenous insulin production. Individuals with established T1DM therefore require lifelong exogenous insulin therapy for survival. [12]

Although extensive research has established the major

contribution of genetic susceptibility to the development of T1DM, the precise role of environmental factors remains incompletely understood. Proposed environmental influences include viral infections, alterations in the gut microbiome, dietary factors, and other environmental exposures; however, the evidence for individual factors remains variable. T1DM is therefore considered a multifactorial disease in which genetic predisposition interacts with environmental and immunological factors to initiate and accelerate pancreatic β-cell destruction.

Type 2 Diabetes Mellitus (T2dm)

Type 2 diabetes mellitus (T2DM), previously referred to as non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, is the most common form of diabetes mellitus and accounts for approximately 90–95% of all diabetes cases. The risk of developing T2DM is influenced by multiple factors, including increasing age, overweight and obesity, physical inactivity, unhealthy dietary patterns, and genetic susceptibility. The risk is also increased in individuals with a previous history of gestational diabetes mellitus (GDM), hypertension, dyslipidaemia, and certain genetic and ethnic backgrounds.

Type 2 diabetes mellitus is primarily characterized by two major pathophysiological abnormalities: insulin resistance and progressive pancreatic β-cell dysfunction. [13-14] These abnormalities develop gradually and interact with one another to produce persistent hyperglycaemia.

Initially, insulin-sensitive tissues, particularly skeletal muscle, liver, and adipose tissue, become resistant to the actions of insulin. In response to insulin resistance, pancreatic β-cells initially increase insulin secretion, resulting in compensatory hyperinsulinemia, which may maintain blood glucose concentrations within or near the normal range during the early stages of the disease. However, persistent metabolic stress gradually impairs β-cell function. As β-cell secretory capacity declines, insulin secretion becomes inadequate to compensate for the existing insulin resistance, resulting in relative insulin deficiency and progressive hyperglycaemia.

Insulin resistance reduces glucose uptake, particularly in skeletal muscle, increases hepatic glucose production, and impairs the normal insulin-mediated suppression of adipose tissue lipolysis. These alterations contribute to elevated circulating glucose and free fatty acid concentrations. Visceral obesity is an important contributor to insulin resistance and is associated with increased release of free fatty acids, pro-inflammatory cytokines, and altered adipokines from adipose tissue. [15] Chronic exposure of pancreatic β-cells and other metabolic tissues to elevated glucose and lipid concentrations results in glucotoxicity and lipotoxicity, which further impair β-cell function and insulin sensitivity. This creates a self-perpetuating cycle that contributes to the progressive deterioration of glucose homeostasis.

In contrast to type 1 diabetes mellitus, endogenous insulin secretion is generally maintained in T2DM and is usually sufficient to suppress ketogenesis and prevent spontaneous diabetic ketoacidosis (DKA). However, DKA can occur in individuals with T2DM under conditions of severe physiological stress, infection, or marked insulin deficiency. Patients with T2DM are at increased risk of both microvascular and macrovascular complications, including diabetic retinopathy, nephropathy, neuropathy, cardiovascular disease, cerebrovascular disease, and peripheral vascular disease.

T2DM is also associated with an increased risk of cognitive impairment and neurodegenerative disorders. Epidemiological studies have reported associations between T2DM and mild cognitive impairment (MCI), dementia, and Alzheimer's disease (AD), potentially involving mechanisms such as chronic hyperglycaemia, insulin resistance, vascular dysfunction, oxidative stress, inflammation, and metabolic abnormalities. [16]

Gestational Diabetes Mellitus (Gdm)

Gestational diabetes mellitus (GDM) is a common metabolic disorder of pregnancy characterized by hyperglycaemia that is first recognized during pregnancy and does not represent overt diabetes that clearly preceded pregnancy. It is most commonly diagnosed during the second or third trimester, when physiological insulin resistance increases substantially. GDM develops when pancreatic β-cells are unable to increase insulin secretion sufficiently to compensate for the insulin resistance associated with pregnancy. [17]

During normal pregnancy, profound metabolic adaptations occur to ensure an adequate supply of nutrients to the developing fetus. As pregnancy progresses, particularly during the second and third trimesters, placental hormones such as human placental lactogen, progesterone, oestrogen, cortisol, and placental growth hormone contribute to increasing maternal insulin resistance. This physiological insulin resistance promotes the availability of glucose and other nutrients to the fetus. In healthy women, pancreatic β-cells respond by increasing insulin synthesis and secretion, thereby maintaining maternal glucose homeostasis. However, women with pre-existing insulin resistance or impaired β-cell function may be unable to compensate adequately for the increased metabolic demand, resulting in maternal hyperglycaemia and the development of GDM. [18]

Glucose metabolism changes throughout pregnancy. During early pregnancy, fasting plasma glucose concentrations may be relatively lower because of increased glucose utilization and other metabolic adaptations. As gestation advances, maternal insulin resistance progressively increases, particularly during the second and third trimesters. Consequently, postprandial glucose concentrations may increase, placing greater demand on pancreatic β-cells. When β-cell compensation becomes insufficient, persistent maternal hyperglycaemia develops and GDM may be diagnosed. [19]

The prevalence of GDM varies considerably between populations because of differences in diagnostic criteria, screening practices, maternal characteristics, ethnicity, and prevalence of obesity. GDM is influenced by a combination of genetic, metabolic, and environmental factors. Important risk factors include advanced maternal age, overweight or obesity, previous GDM, a family history of diabetes mellitus, previous delivery of a macrossomic infant, polycystic ovary syndrome, physical inactivity, and impaired glucose tolerance. [20]

Maternal obesity is one of the most important modifiable risk factors for GDM. Increasing maternal body mass index (BMI) is associated with a progressively greater risk of developing GDM. Excess adiposity, particularly visceral adiposity, promotes insulin resistance through alterations in adipokine secretion, increased free fatty acid availability, and chronic low-grade inflammation. These metabolic

abnormalities increase the demand for insulin and may contribute to inadequate β-cell compensation during pregnancy. Maternal obesity is also associated with an increased risk of adverse pregnancy outcomes affecting both the mother and fetus. [17]

GDM is associated with several adverse maternal and fetal outcomes. Maternal complications include gestational hypertension, pre-eclampsia, increased risk of caesarean delivery, and future development of type 2 diabetes mellitus. Fetal and neonatal complications may include excessive fetal growth (macrosomia), large-for-gestational-age birth, neonatal hypoglycaemia, birth trauma, and respiratory complications. The offspring of mothers with GDM may also have an increased long-term risk of obesity, impaired glucose metabolism, and type 2 diabetes mellitus. [17]

Although maternal glucose metabolism generally improves after delivery, GDM identifies women who are at increased risk of developing type 2 diabetes mellitus later in life. The risk is particularly important because the metabolic abnormalities associated with insulin resistance and β-cell dysfunction may persist after pregnancy. Women with previous GDM are also at increased risk of developing GDM in subsequent pregnancies. Therefore, postpartum glucose testing and long-term periodic screening for diabetes and prediabetes are important components of follow-up care. [21-22]

Management of GDM aims to maintain maternal blood glucose within the recommended target range and minimize adverse maternal and fetal outcomes. Medical nutrition therapy, appropriate physical activity, weight management, and regular blood glucose monitoring form the basis of initial management. If adequate glycaemic control cannot be achieved through lifestyle measures alone, pharmacological treatment may be required. Insulin remains an established pharmacological treatment for GDM, while the use of oral glucose-lowering agents may depend on clinical circumstances and local guidelines. Regular maternal and fetal monitoring is also important throughout pregnancy.

Early detection and appropriate management of GDM are essential for reducing pregnancy-related complications and improving both short- and long-term health outcomes. Because GDM is also an important predictor of future type 2 diabetes mellitus, its diagnosis provides an opportunity for long-term preventive strategies, including sustained lifestyle modification, maintenance of healthy body weight, and regular metabolic screening.

Prediabetes

Prediabetes is an intermediate state of dysglycaemia between normal glucose regulation and type 2 diabetes mellitus (T2DM). It is characterized by impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and/or elevated glycated haemoglobin (HbA1c) levels that are above the normal range but below the diagnostic threshold for diabetes mellitus. [23] Prediabetes shares several pathophysiological mechanisms with T2DM, particularly insulin resistance and progressive pancreatic β-cell dysfunction. Additional metabolic abnormalities include increased lipolysis, impaired incretin response, inadequate suppression of glucagon secretion, reduced hepatic glucose uptake, increased hepatic glucose production, and abnormalities in renal glucose and sodium handling. [24] Collectively, these abnormalities contribute to progressive dysglycaemia and increase the risk of developing T2DM and associated cardiovascular and metabolic complications. [25]

The development of prediabetes is influenced by a combination of demographic, genetic, behavioural, metabolic, and inflammatory factors. Important risk factors include increasing age, family history of diabetes, overweight and obesity, abdominal adiposity, physical inactivity, unhealthy dietary patterns, hypertension, dyslipidaemia, insulin resistance, impaired β-cell function, hepatic steatosis, albuminuria, elevated inflammatory markers, and reduced adiponectin concentrations. [26] Emerging risk factors include alterations in amino acid and lipid metabolism, genetic susceptibility such as variants in the TCF7L2 gene, gut microbiome dysbiosis, and transcriptomic alterations, including changes in microRNA expression. [27]

Early identification of prediabetes provides an important opportunity for preventive intervention. Lifestyle modification, including weight management, a healthy diet, and regular physical activity, can substantially reduce the risk of progression from prediabetes to T2DM.

Latent Autoimmune Diabetes in Adults (Lada)

Latent autoimmune diabetes in adults (LADA) is a slowly progressive form of autoimmune diabetes that shares clinical characteristics with both type 1 diabetes mellitus (T1DM) and T2DM. [28] It is characterized by immune-mediated destruction of pancreatic β-cells and is commonly associated with the presence of glutamic acid decarboxylase autoantibodies (GADA). [29] Unlike classical T1DM, β-cell destruction in LADA progresses more slowly, allowing residual endogenous insulin secretion during the early stages of disease. [30]

Insulin resistance may also contribute to the development and progression of LADA, although its degree is generally lower than that observed in typical T2DM. [29] The combined effects of progressive β-cell dysfunction and insulin resistance eventually result in persistent hyperglycaemia and, in many patients, the need for insulin therapy.

The development of LADA is believed to involve an interaction between genetic susceptibility, autoimmune mechanisms, and environmental factors. [31] Genetic susceptibility is strongly associated with HLA class II genes, particularly HLA-DR and HLA-DQ haplotypes. Other genes, including PTPN22, INS, SH2B3, and TCF7L2, have also been implicated in susceptibility to LADA. Lifestyle and metabolic factors, including overweight or obesity and physical inactivity, may contribute to insulin resistance and disease progression. Smoking has also been associated with an increased risk in some studies, although findings have not been completely consistent. [32]

Maturity-Onset Diabetes Of The Young (Mody)

Maturity-onset diabetes of the young (MODY) is a heterogeneous group of monogenic diabetes disorders caused by pathogenic variants in a single gene involved in pancreatic β-cell development, glucose sensing, or insulin secretion. MODY is generally inherited in an autosomal dominant pattern and commonly presents at a young age, often before 25 years. [33]

MODY is relatively uncommon and accounts for a small proportion of diabetes cases. [34] It may account for approximately 1–6% of diabetes diagnosed in children and young adults, although estimates vary among populations and diagnostic approaches. [35] A characteristic family history, with diabetes occurring across successive generations, may

provide an important clue to the diagnosis. [36]

Unlike T1DM, MODY is not primarily an autoimmune disorder. Unlike typical T2DM, significant insulin resistance is generally absent, and the principal abnormality is impaired glucose-stimulated insulin secretion. MODY comprises several genetic subtypes caused by variants in different genes, and the clinical presentation and appropriate treatment vary according to the specific genetic defect. [34, 37-39] Genetic testing is therefore important for confirming the diagnosis and guiding individualized management.

Neonatal Diabetes Mellitus

Neonatal diabetes mellitus (NDM) is a rare form of monogenic diabetes that presents during the first six months of life. It is caused primarily by genetic abnormalities affecting pancreatic β-cell development, insulin synthesis, or insulin secretion. Some forms are associated with abnormalities of the ATP-sensitive potassium (KATP) channel, which plays an important role in glucose-stimulated insulin secretion. [40, 41]

The pathological abnormalities may include reduced pancreatic β-cell mass, impaired insulin synthesis, defective insulin secretion, or developmental abnormalities of the pancreas. Neonatal diabetes is broadly classified into two major forms:

1. Transient Neonatal Diabetes Mellitus

Transient neonatal diabetes mellitus (TNDM) usually resolves during infancy, often within the first several months of life. However, affected individuals may develop diabetes again later in childhood, adolescence, or adulthood. [42]

2. Permanent Neonatal Diabetes Mellitus

Permanent neonatal diabetes mellitus (PNDM) persists throughout life and requires long-term management. Identification of the underlying genetic abnormality is important because some genetic forms respond particularly well to specific pharmacological therapies.

Brittle Diabetes

Brittle diabetes, also referred to as labile diabetes, describes a severe form of diabetes characterized by frequent, unpredictable, and difficult-to-control fluctuations in blood glucose concentrations. Patients may experience recurrent episodes of severe hyperglycaemia, hypoglycaemia, and, in some cases, diabetic ketoacidosis (DKA). Brittle diabetes is not considered a separate type of diabetes and is most commonly associated with T1DM or severe insulin-deficient diabetes. [42, 43]

Several factors may contribute to brittle diabetes, including psychological or psychiatric disorders, eating disorders, impaired awareness of hypoglycaemia, coexisting medical conditions, malabsorption, irregular food intake, difficulties with insulin administration, and limited access to insulin, food, or healthcare. Early identification of contributing factors and a multidisciplinary approach involving diabetes specialists, dietitians, mental health professionals, and other healthcare providers can improve glycaemic control and reduce complications. [42, 43]

Diagnosis of Diabetes Mellitus

Diabetes mellitus is diagnosed using biochemical criteria based on plasma glucose concentrations and/or glycated haemoglobin (HbA1c). The principal diagnostic tests include fasting plasma glucose (FPG), the 2-hour plasma glucose concentration during a 75-g oral glucose tolerance test (OGTT), HbA1c, and random plasma glucose in individuals with characteristic symptoms of hyperglycaemia or hyperglycaemic crisis. [43]

1. Fasting Plasma Glucose (FPG)

Fasting plasma glucose is measured after an overnight fast of at least 8 hours. According to commonly used diagnostic criteria, an FPG concentration of <100 mg/dL (<5.6 mmol/L) is considered normal, 100–125 mg/dL (5.6–6.9 mmol/L) indicates impaired fasting glucose/prediabetes, and ≥126 mg/dL (≥7.0 mmol/L) is diagnostic of diabetes when confirmed appropriately. FPG is relatively inexpensive, convenient, and widely used for screening and diagnosis. [43, 45]

2. Oral Glucose Tolerance Test (OGTT)

The oral glucose tolerance test assesses the body's ability to regulate glucose following ingestion of 75 g of anhydrous glucose. A 2-hour plasma glucose concentration of ≥200 mg/dL (≥11.1 mmol/L) is diagnostic of diabetes. A 2-hour value of 140–199 mg/dL (7.8–11.0 mmol/L) indicates impaired glucose tolerance. Although OGTT is more sensitive than FPG in identifying certain abnormalities of glucose metabolism, it is less convenient because it requires fasting and a prolonged testing period. [43, 45]

3. Glycated Haemoglobin (HbA1c)

HbA1c reflects average blood glucose exposure over approximately the preceding 2–3 months and does not require fasting. An HbA1c value of ≥6.5% is consistent with diabetes, whereas 5.7–6.4% indicates prediabetes. HbA1c has relatively low biological variability and is convenient for diagnosis and monitoring. However, conditions affecting red blood cell turnover or haemoglobin may influence HbA1c results and should be considered when interpreting the test. [44]

4. Random Plasma Glucose

A random plasma glucose concentration of ≥200 mg/dL (≥11.1 mmol/L) in an individual with classic symptoms of hyperglycaemia, such as polyuria, polydipsia, unexplained weight loss, or symptoms of hyperglycaemic crisis, can establish the diagnosis of diabetes. [43]

5. Confirmation of Diagnosis

In individuals without unequivocal hyperglycaemia or a hyperglycaemic crisis, an abnormal diagnostic test should generally be confirmed by repeating the same test or by performing another accepted diagnostic test. Confirmation is generally unnecessary when marked hyperglycaemia is accompanied by classic symptoms or hyperglycaemic crisis. [43]

6. Diagnostic Criteria for Prediabetes

Prediabetes represents an intermediate state of dysglycaemia and is associated with an increased risk of progression to T2DM and cardiovascular disease. Commonly used criteria include:

Table 1

Test	Normal	Prediabetes	Diabetes
FPG	<100 mg/dL	100–125 mg/dL	≥126 mg/dL
2-h OGTT	<140 mg/dL	140–199 mg/dL	≥200 mg/dL
HbA1c	<5.7%	5.7–6.4%	≥6.5%

Early identification of prediabetes enables timely lifestyle intervention and risk-factor modification, which can delay or prevent progression to T2DM. [3, 43]

Complications of Diabetes Mellitus

Diabetes mellitus is a chronic metabolic disorder that can produce both acute and chronic complications when glycaemic control is inadequate. These complications can affect multiple organ systems and contribute substantially to morbidity, disability, and mortality.

1. Acute Complications

- **Hypoglycaemia**

Hypoglycaemia refers to an abnormally low blood glucose concentration and is most commonly associated with insulin or certain glucose-lowering medications. Clinical manifestations include tremor, sweating, palpitations, hunger, dizziness, confusion, and behavioural changes. Severe hypoglycaemia can result in seizures, loss of consciousness, and potentially death. Prompt administration of rapidly absorbable carbohydrate is required in conscious individuals, while severe episodes may require emergency treatment with glucagon or intravenous glucose.

- **Diabetic Ketoacidosis**

Diabetic ketoacidosis (DKA) is an acute metabolic emergency characterized by hyperglycaemia, ketosis, and metabolic acidosis. It occurs most commonly in T1DM but can also occur in individuals with T2DM under conditions of severe insulin deficiency or physiological stress. Common precipitating factors include infection, inadequate insulin administration, and acute illness.

- **Hyperosmolar Hyperglycaemic State**

Hyperosmolar hyperglycaemic state (HHS) is a serious acute complication characterized by severe hyperglycaemia, increased plasma osmolality, and profound dehydration, usually with little or no significant ketoacidosis. It occurs more commonly in individuals with T2DM and may result in altered mental status, coma, and death if not treated promptly.

2. Chronic Complications

Chronic complications develop progressively as a consequence of prolonged metabolic abnormalities, particularly persistent hyperglycaemia, oxidative stress, inflammation, and vascular dysfunction. They are broadly divided into microvascular and macrovascular complications.

A. Microvascular Complications

- **Diabetic Nephropathy**

Persistent hyperglycaemia damages the renal microvasculature and glomerular structures, leading to albuminuria, progressive decline in renal function, chronic kidney disease, and, in severe cases, kidney failure.

- **Diabetic Retinopathy**

Diabetic retinopathy results from chronic damage to the retinal microvasculature. Progressive retinal vascular injury may lead to macular oedema, retinal ischaemia, abnormal blood vessel formation, visual impairment, and, in advanced cases, blindness.

- **Diabetic Neuropathy**

Diabetic neuropathy results from metabolic and vascular injury to peripheral and autonomic nerves. Symptoms may include pain, numbness, tingling, loss of sensation, and weakness, particularly in the lower limbs. Autonomic neuropathy may affect gastrointestinal, cardiovascular, genitourinary, and sexual function.

B. Macrovascular Complications

- **Cardiovascular disease**

Diabetes significantly increases the risk of atherosclerotic cardiovascular disease, including coronary artery disease, myocardial infarction, and heart failure. Hypertension and dyslipidaemia frequently coexist with diabetes and further increase cardiovascular risk.

- **Cerebrovascular Disease**

Individuals with diabetes have an increased risk of ischaemic stroke and other cerebrovascular disorders, partly due to accelerated atherosclerosis and endothelial dysfunction.

- **Peripheral Artery Disease**

Peripheral artery disease (PAD) results from atherosclerotic narrowing of peripheral arteries and can reduce blood flow to the lower limbs. It may contribute to claudication, poor wound healing, tissue ischaemia, and limb-threatening disease.

- **Diabetic Foot Complications**

Diabetic foot complications arise from the combined effects of peripheral neuropathy, peripheral arterial disease, impaired immunity, and poor wound healing. These factors increase the risk of foot ulcers, infection, tissue necrosis, and lower-limb amputation.

C. Other Complications

- **Gastroparesis**

Diabetic autonomic neuropathy can impair gastric motility and result in gastroparesis, characterized by delayed gastric emptying. Clinical manifestations include nausea, vomiting, early satiety, bloating, and unpredictable postprandial glucose excursions.

- **Increased Susceptibility to Infection**

Diabetes is associated with impaired immune and inflammatory responses, increasing susceptibility to certain infections, including urinary tract, skin, and soft-tissue infections. Hyperglycaemia may further impair host defence mechanisms.

- **Skin Complications**

Individuals with diabetes may develop several cutaneous

manifestations, including diabetic dermopathy, bacterial and fungal infections, and impaired wound healing.

- **Cognitive and Mental Health Complications**

Diabetes has been associated with an increased risk of cognitive impairment and dementia. Chronic hyperglycaemia, insulin resistance, vascular dysfunction, oxidative stress, and inflammation may contribute to these neurological outcomes. Diabetes is also associated with an increased burden of psychological conditions such as depression and anxiety, which may adversely affect self-care and glycaemic management. [46, 47]

Appropriate glycaemic control, regular monitoring, healthy dietary practices, physical activity, pharmacological therapy, and screening for complications can substantially reduce the risk of diabetes-related morbidity. Early detection and management are essential for preventing or delaying the progression of both microvascular and macrovascular complications.

Prevention and Management of Diabetes Mellitus

1. Prevention of Type 2 Diabetes Mellitus

The primary prevention of T2DM focuses on reducing modifiable risk factors in individuals at increased risk of developing the disease. Regular physical activity, healthy dietary patterns, maintenance of a healthy body weight, and prevention or reduction of excess adiposity are fundamental components of diabetes prevention.

Dietary patterns emphasizing whole grains, vegetables, fruits, legumes, dietary fibre, nuts, and unsaturated fats, while limiting refined carbohydrates, added sugars, saturated fats, and highly processed foods, can improve metabolic health and reduce the risk of T2DM. Regular physical activity improves insulin sensitivity, assists weight management, and reduces cardiovascular risk.

2. Lifestyle Management

Lifestyle modification is an essential component of T2DM management. In individuals who are overweight or obese, clinically meaningful weight reduction can improve insulin sensitivity and glycaemic control. Regular aerobic and resistance exercise can improve glucose utilization and metabolic health.

In individuals with prediabetes, structured lifestyle intervention involving dietary modification, weight reduction, and regular physical activity can substantially reduce the risk of progression to T2DM. The Diabetes Prevention Program (DPP) demonstrated that intensive lifestyle intervention reduced the incidence of T2DM by approximately 58% compared with placebo in high-risk individuals. [50]

3. Pharmacological Management

Pharmacological treatment is individualized according to glycaemic status, cardiovascular and renal comorbidities, body weight, risk of hypoglycaemia, patient preferences, and other clinical factors.

Major classes of glucose-lowering medications include:

- Biguanides, particularly metformin
- Sulfonylureas
- Thiazolidinediones
- α-Glucosidase inhibitors
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Glucagon-like peptide-1 (GLP-1) receptor agonists
- Sodium-glucose cotransporter-2 (SGLT2) inhibitors
- Insulin and other injectable therapies

The selection of therapy should be individualized rather than based solely on glucose-lowering efficacy. Particular drug classes may provide additional cardiovascular, renal, or weight-related benefits in appropriate patients.

4. Insulin Therapy

Insulin therapy is essential for individuals with T1DM because of absolute insulin deficiency. It is also used in T2DM when adequate glycaemic control cannot be achieved with lifestyle modification and non-insulin pharmacological therapy, or when severe hyperglycaemia, catabolic symptoms, acute illness, pregnancy, or other clinical circumstances warrant insulin treatment.

5. Prevention of Progression from Prediabetes to Diabetes

Individuals with prediabetes or a high risk of developing T2DM should receive structured interventions aimed at weight reduction, increased physical activity, and dietary modification. Pharmacological prevention may be considered in selected high-risk individuals, particularly when lifestyle intervention alone is insufficient. Metformin has demonstrated efficacy in delaying the development of T2DM in selected individuals with prediabetes. Other pharmacological approaches, including weight-management therapies, may also reduce diabetes risk in appropriate patients.

Overall, effective prevention and management of diabetes require a multidisciplinary and patient-centred approach that combines lifestyle modification, regular monitoring, appropriate pharmacological therapy, management of cardiovascular and metabolic risk factors, and early detection and treatment of diabetes-related complications.

Recent Advances / Novel Therapeutic Approaches In Diabetes Mellitus

Recent advances in diabetes research have shifted the therapeutic approach from conventional glucose lowering toward individualized, mechanism-based treatment aimed at improving glycaemic control while reducing cardiovascular, renal, metabolic, and other long-term complications. The development of incretin-based therapies, sodium-glucose cotransporter-2 (SGLT2) inhibitors, novel insulin formulations, immune-modifying therapies, and stem cell-derived β-cell replacement strategies has substantially expanded the therapeutic landscape of diabetes mellitus. In addition, continuous glucose monitoring (CGM), automated insulin-delivery systems, and digital health technologies have improved personalized diabetes management.

1. Incretin-Based Therapies

Incretin-based therapies have become an important component of the modern treatment of type 2 diabetes mellitus (T2DM). Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) enhance glucose-dependent insulin secretion, suppress inappropriate glucagon secretion, delay gastric emptying, and promote satiety, thereby improving glycaemic control and reducing body weight. Their clinical importance has expanded beyond glucose lowering because several agents have demonstrated cardiovascular benefits.

Semaglutide is one of the most extensively studied GLP-1 receptor agonists. In the FLOW trial, semaglutide significantly reduced clinically important kidney outcomes and cardiovascular mortality in individuals with T2DM and chronic kidney disease. The primary kidney/cardiovascular composite outcome was reduced by approximately 24% compared with placebo. [51] The cardiovascular benefits of semaglutide have also been demonstrated with oral administration. In the SOUL trial, oral semaglutide reduced major adverse cardiovascular events by approximately 14% compared with placebo in people with T2DM and established atherosclerotic cardiovascular disease, chronic kidney disease, or both. [52]

These findings have contributed to a change in the therapeutic concept of diabetes management, in which glucose-lowering therapy is increasingly selected according to cardiovascular and renal risk as well as glycaemic efficacy.

2. Dual GIP/GLP-1 Receptor Agonists

A major recent development is the use of dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonists. Tirzepatide is the first widely established dual GIP/GLP-1 receptor agonist and produces substantial reductions in HbA1c and body weight. GIP and GLP-1 receptor activation enhances glucose-dependent insulin secretion while reducing glucagon secretion and food intake. Beyond its effects on glycaemia and body weight, cardiovascular outcomes with tirzepatide have recently been investigated. In the SURPASS-CVOT trial, tirzepatide was noninferior to dulaglutide for the composite of cardiovascular death, myocardial infarction, or stroke in patients with T2DM and atherosclerotic cardiovascular disease. [53] These findings further support the development of incretin-based therapies as important components of cardiometabolic disease management.

3. Emerging Triple Hormone-Receptor Agonists

Retatrutide is an investigational triple agonist targeting the GIP, GLP-1, and glucagon receptors. By simultaneously influencing multiple metabolic pathways, this approach aims to improve glucose metabolism, increase energy expenditure, suppress appetite, and promote substantial weight reduction. Early clinical studies have demonstrated marked weight loss, supporting further investigation of triple-hormone receptor agonists for obesity and metabolic disease. [54]

Although retatrutide remains an investigational therapy, multi-receptor agonism represents an important direction in the development of future treatments for T2DM and obesity.

4. SGLT2 Inhibitors and Cardiorenal Protection

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, including empagliflozin, dapagliflozin, and canagliflozin, have transformed the management of T2DM by demonstrating benefits that extend beyond glucose lowering. These agents reduce renal glucose reabsorption, increase urinary glucose excretion, and produce modest reductions in body weight and blood pressure.

The therapeutic role of SGLT2 inhibitors has increasingly expanded toward cardiorenal protection, particularly in patients with heart failure or chronic kidney disease. Their ability to slow progression of chronic kidney disease and reduce cardiovascular risk has made them an important component of contemporary diabetes and cardiorenal management. [55]

However, SGLT2 inhibitors require careful patient selection. In individuals with T1DM, clinical trials have demonstrated improvements in glycaemic control and body weight but also an increased risk of diabetic ketoacidosis. Consequently, SGLT2 inhibitors are not approved for routine treatment of T1DM in the United States. [56]

5. Novel Long-Acting and Once-Weekly Insulin Formulations

The development of once-weekly basal insulin formulations represents an important advance in insulin therapy. Insulin icodec and insulin efsitora alfa have been designed to provide prolonged basal insulin action, potentially reducing injection frequency and improving treatment acceptance and adherence.

Clinical studies have shown that once-weekly insulin can provide glycaemic control comparable to once-daily basal insulin in individuals with T2DM. [57,58] In a 2025 phase 3 trial, once-weekly insulin efsitora was noninferior to once-daily insulin glargine in reducing HbA1c in adults with T2DM who had not previously received insulin therapy.[58]

Reducing the number of injections from approximately 365 per year to 52 per year may simplify insulin treatment and potentially improve treatment satisfaction and persistence.

6. Immunotherapy for Type 1 Diabetes Mellitus

A major advance in T1DM treatment is the development of therapies directed toward the underlying autoimmune process rather than glucose control alone. Teplizumab, an anti-CD3 monoclonal antibody, modulates T-cell activity and has been shown to delay the progression from stage 2 T1DM to symptomatic stage 3 disease.

In a landmark clinical trial, teplizumab delayed the median time to diagnosis of clinical T1DM from approximately 24.4 months to 48.4 months, corresponding to a hazard ratio of 0.41 compared with placebo.[59] The U.S. Food and Drug Administration subsequently approved teplizumab for delaying the onset of stage 3 T1DM in appropriate high-risk individuals with stage 2 disease.[60]

This approach represents a significant change in the treatment paradigm because it demonstrates that disease progression can be modified before symptomatic T1DM develops.

7. Stem Cell-Derived β-Cell Replacement Therapy

Replacement of insulin-producing β-cells represents another promising approach for T1DM. Conventional pancreatic or donor-islet transplantation is limited by donor availability and the requirement for immunosuppression. Advances in stem-cell technology have enabled the development of stem cell-derived pancreatic islet cells that may provide a renewable source of insulin-producing cells.

A 2025 phase 1–2 study of zimislecel, an allogeneic stem cell-derived islet-cell therapy, demonstrated restoration of islet function in individuals with T1DM. In the full-dose cohort, all 12 participants were free from severe hypoglycaemic events and achieved HbA1c levels below 7%; 10 of 12 participants achieved insulin independence at 1 year.[61] Although these findings are promising, larger and longer studies are required to establish long-term efficacy, safety, durability, and the optimal approach to immunosuppression.

8. Donor-Derived Islet Cell Therapy

Cell replacement therapy has also entered clinical practice for selected individuals with severe T1DM. In 2023, the U.S. FDA approved donislecel-jujn (Lantidra), an allogeneic pancreatic islet cellular therapy derived from deceased donors. It is indicated for selected adults with T1DM who are unable to achieve target HbA1c because of recurrent severe hypoglycaemia despite intensive diabetes management and education.[62]

Although donor-derived islet transplantation can restore endogenous insulin secretion in selected patients, its broader use is limited by donor availability, immunological rejection, and the need for immunosuppressive therapy. Therefore, stem cell-derived islet replacement remains an important area of ongoing research.

9. Artificial Pancreas and Automated Insulin Delivery

Technological advances have substantially improved the management of T1DM. Continuous glucose monitoring (CGM) provides real-time or intermittently scanned measurements of glucose concentrations and allows patients and clinicians to assess time in range, glucose variability, and hypoglycaemic episodes.

Integration of CGM with insulin pumps has led to the development of automated insulin-delivery systems, commonly referred to as artificial pancreas or hybrid closed-loop systems. These systems use glucose sensor data and algorithm-based insulin adjustment to reduce both hyperglycaemia and hypoglycaemia. Increasing automation has reduced the burden of diabetes self-management and improved glycaemic outcomes in many individuals with T1DM.

10. Digital Health and Artificial Intelligence

Digital health technologies are increasingly being incorporated into diabetes management. Mobile health applications, connected glucose meters, remote monitoring platforms, wearable devices, and cloud-based data sharing facilitate continuous communication between patients and healthcare professionals.

Artificial intelligence (AI) and machine-learning approaches are also being investigated for prediction of hypoglycaemia, identification of glucose patterns, individualized insulin dosing, risk prediction, and interpretation of large-scale continuous glucose monitoring datasets. These approaches may facilitate precision diabetes care by integrating clinical, behavioural, metabolic, and glucose-monitoring data.

11. Emerging β-Cell Preservation Strategies

Because progressive loss of pancreatic β-cell function is a major component of T2DM and T1DM, preservation of β-cell function is an important therapeutic objective. Research is investigating agents capable of reducing β-cell stress, inflammation, oxidative injury, and immune-mediated destruction.

In T1DM, immunomodulatory therapies aim to preserve residual β-cell function by reducing autoimmune destruction. In T2DM, metabolic interventions that reduce glucotoxicity and lipotoxicity may help preserve β-cell function. Several experimental approaches targeting inflammatory pathways, cellular stress mechanisms, and β-cell regeneration are currently under investigation.

12. Precision Medicine in Diabetes

Diabetes is increasingly recognized as a heterogeneous group of disorders rather than a single disease. Advances in genomics, metabolomics, transcriptomics, and artificial intelligence may allow patients to be classified according to their underlying biological characteristics.

Precision medicine aims to select treatment according to individual patient characteristics, including genetic susceptibility, β-cell function, insulin resistance, obesity phenotype, cardiovascular risk, kidney function, and response to previous therapies. This approach may improve therapeutic efficacy while minimizing adverse effects and unnecessary treatment.

13. Future Therapeutic Directions

Future diabetes treatment is likely to move increasingly toward disease modification and integrated cardiometabolic management, rather than glucose lowering alone. Major areas of investigation include stem-cell-derived β-cell replacement, immune tolerance induction, gene-based approaches, multi-hormonal receptor agonists, novel insulin formulations, β-cell regeneration, and AI-assisted individualized treatment.

The combination of pharmacological, cellular, immunological, and digital technologies may ultimately enable more durable restoration of metabolic control and reduce the long-term complications associated with diabetes mellitus.

Conclusion

Diabetes mellitus is a complex and heterogeneous metabolic disorder whose global burden continues to increase. The disease encompasses distinct forms with different underlying mechanisms, including autoimmune β-cell destruction in type 1 diabetes, insulin resistance and progressive β-cell dysfunction in type 2 diabetes, pregnancy-associated metabolic abnormalities in gestational diabetes, and specific genetic or autoimmune forms such as MODY, neonatal diabetes, and LADA. Prediabetes provides an important window for early intervention because appropriate lifestyle modification and risk-factor management can delay or prevent the progression to overt diabetes.

Persistent hyperglycaemia is associated with serious acute and chronic complications that can affect multiple organ systems and substantially reduce quality of life. Therefore, early diagnosis, regular monitoring, individualized glycaemic targets, and comprehensive management of cardiovascular, renal, metabolic, and other risk factors are essential. Current diabetes management has moved beyond conventional glucose lowering toward a broader cardio-renal-metabolic and patient-centred approach, with treatment selection increasingly based on individual comorbidities, complications, weight, risk of hypoglycaemia, and patient preferences.

The therapeutic landscape of diabetes has undergone substantial transformation with the introduction of GLP-1 receptor agonists, dual GIP/GLP-1 receptor agonists, SGLT2 inhibitors, advanced insulin formulations, and technology-assisted diabetes management. Emerging approaches such as immunotherapy for T1DM, stem-cell-derived β-cell replacement, automated insulin-delivery systems, continuous glucose monitoring, and artificial intelligence-based diabetes care offer further opportunities for improving disease

outcomes. The 2026 standards of care also emphasize broader use of diabetes technologies, individualized obesity treatment, and therapies that provide benefits beyond glycaemic control, including cardiovascular, kidney, and metabolic protection.

Despite these advances, important challenges remain, including increasing disease prevalence, disparities in access to healthcare and newer therapies, treatment adherence, obesity, and the long-term prevention of complications. Future research should focus on disease-modifying therapies, preservation and restoration of pancreatic β-cell function, immune tolerance, stem-cell-based treatments, precision medicine, and integration of digital and artificial intelligence technologies. A multidisciplinary, preventive, and individualized approach combining lifestyle modification with appropriate pharmacological and technological interventions will remain essential for reducing the global burden of diabetes mellitus and improving long-term patient outcomes.

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