DIABETES MELLITUS: PATHOPHYSIOLOGY, CLASSIFICATION, DIAGNOSIS, TREATMENT, AND NEW TREATMENT APPROACHES

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Abstract

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It has emerged as a major global health concern due to its rapidly increasing prevalence and associated microvascular and macrovascular complications. The present review discusses the pathophysiology, classification, clinical manifestations, diagnostic approaches, and current treatment strategies for diabetes mellitus. The review highlights the role of insulin resistance, β-cell dysfunction, inflammation, oxidative stress, and genetic as well as environmental factors in disease progression. Conventional management approaches including lifestyle modification, insulin therapy, oral antidiabetic drugs, and combination therapies are comprehensively discussed. Furthermore, recent advances such as GLP-1 receptor agonists, SGLT2 inhibitors, stem cell therapy, gene therapy, nanotechnology-based drug delivery systems, artificial pancreas technology, and precision medicine have been explored as emerging therapeutic strategies. The review also emphasizes the potential role of herbal and natural therapeutics, including medicinal plants and bioactive phytoconstituents, in diabetes management. Despite substantial progress in therapeutic development, challenges related to safety, accessibility, long-term efficacy, and cost remain significant. Overall, continued research and multidisciplinary approaches are essential for developing safer, more effective, and personalized therapeutic interventions for diabetes mellitus.

Keywords: *Diabetes Mellitus; Hyperglycemia; Insulin resistance; β-cell dysfunction; Antidiabetic drugs; GLP-1 receptor agonists; SGLT2 inhibitors*

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1. Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia caused by impaired insulin secretion, insulin action, or both. It is one of the most common non-communicable diseases worldwide and represents a major public health challenge due to its increasing prevalence, long-term complications, and economic burden. The disease affects carbohydrate, fat, and protein metabolism and may lead to severe complications involving the cardiovascular system, kidneys, eyes, and nerves (DeFronzo et al., 2015).

The global incidence of diabetes has risen significantly because of urbanization, sedentary lifestyle, obesity, unhealthy dietary habits, and aging populations. Type 2 diabetes mellitus is the most prevalent form and is mainly associated with insulin resistance, whereas type 1 diabetes mellitus results from autoimmune destruction of pancreatic β-cells leading to insulin deficiency (Saeedi et al., 2019).

The pathogenesis of diabetes involves genetic, environmental, inflammatory, and oxidative stress-related factors. Chronic hyperglycemia contributes to microvascular complications such as neuropathy, nephropathy, and retinopathy, as well as macrovascular complications including cardiovascular disease and stroke (Forbes & Cooper, 2013). Early diagnosis and proper glycemic control are therefore essential for preventing disease progression and associated complications.

Current management strategies include lifestyle modification, insulin therapy, oral antidiabetic drugs, and combination therapies. Recent advances such as GLP-1 receptor agonists, SGLT2 inhibitors, stem cell therapy, gene therapy, nanotechnology-based drug delivery, and artificial pancreas systems have improved diabetes management (Davies et al., 2022). In addition, herbal therapeutics and precision medicine approaches are gaining attention for their potential role in personalized diabetes care. This review discusses the pathophysiology, classification, diagnosis, treatment approaches, and emerging therapeutic strategies for diabetes mellitus.

2. Pathophysiology of Diabetes Mellitus

Diabetes mellitus is a complex metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The pathophysiology of diabetes involves multiple interrelated mechanisms including insulin resistance, pancreatic β-cell dysfunction, chronic inflammation, oxidative stress, and genetic as well as environmental influences. These abnormalities disrupt glucose homeostasis and contribute to the development and progression of both type 1 and type 2 diabetes mellitus (DeFronzo et al., 2015).

2.1 Insulin Resistance

Insulin resistance is a pathological condition in which peripheral tissues such as skeletal muscle, liver, and adipose tissue exhibit decreased responsiveness to insulin, leading to impaired glucose uptake and increased hepatic glucose production. It is a major pathogenic factor in type 2 diabetes mellitus and is strongly associated with obesity, particularly visceral adiposity. Excess adipose tissue releases free fatty acids, adipokines, and pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which disrupt insulin signaling pathways and impair glucose metabolism (Wilcox, 2005). Additionally, defects in insulin receptor substrate signaling and reduced translocation of glucose transporter type 4 (GLUT4) contribute to decreased insulin sensitivity (Kahn et al., 2006). Initially, pancreatic β-cells compensate by increasing insulin secretion, resulting in hyperinsulinemia; however, prolonged insulin resistance eventually leads to β-cell dysfunction, persistent hyperglycemia, and the development of overt diabetes mellitus (Petersen & Shulman, 2018).

2.2 β-Cell Dysfunction

Pancreatic β-cells are responsible for insulin synthesis and secretion in response to blood glucose levels, and their dysfunction plays a central role in the development and progression of diabetes mellitus. In type 1 diabetes mellitus, autoimmune destruction of β-cells leads to absolute insulin deficiency, whereas in type 2 diabetes mellitus, chronic metabolic stress gradually impairs β-cell function and survival (Cerf, 2013). Multiple factors including glucotoxicity, lipotoxicity, oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, and amyloid deposition contribute to β-cell damage and reduced insulin secretory capacity (Prentki & Nolan, 2006). Chronic hyperglycemia impairs insulin gene expression and insulin release, while elevated free fatty acids promote β-cell apoptosis. As β-cell dysfunction progresses, insulin secretion becomes inadequate to compensate for insulin resistance, resulting in persistent hyperglycemia and progression of diabetes mellitus.

2.3 Role of Inflammation and Oxidative Stress

Chronic low-grade inflammation and oxidative stress play significant roles in the initiation and progression of diabetes mellitus. Adipose tissue in obese individuals acts as an active endocrine organ that releases pro-inflammatory mediators such as TNF-α, IL-1β, and IL-6. These cytokines disrupt insulin signaling pathways and promote insulin resistance (Donath & Shoelson, 2011).

Oxidative stress results from an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms. Hyperglycemia enhances ROS generation through several pathways including glucose auto-oxidation, advanced glycation end-product formation, and mitochondrial dysfunction. Excess ROS damages cellular proteins, lipids, and

DNA, thereby impairing insulin signaling and pancreatic β-cell function (Maritim et al., 2003).

Pancreatic β-cells are particularly susceptible to oxidative stress because of their relatively low antioxidant enzyme activity. Continuous oxidative damage contributes to β-cell apoptosis and decreased insulin secretion. Inflammation and oxidative stress therefore interact synergistically to accelerate diabetes progression and its associated complications.

2.4 Genetic and Environmental Factors

Both genetic and environmental factors play important roles in the development of diabetes mellitus. Several genes associated with insulin secretion, insulin sensitivity, and immune regulation have been linked to diabetes susceptibility. In type 2 diabetes mellitus, genetic variations in genes such as *TCF7L2*, *PPARG*, and *KCNJ11* are strongly associated with impaired glucose metabolism and increased disease risk (Ali, 2013). Type 1 diabetes mellitus has a strong autoimmune and genetic basis, particularly involving human leukocyte antigen (HLA) genes; however, environmental triggers including viral infections, dietary factors, and early-life exposures may initiate autoimmune β-cell destruction in genetically predisposed individuals (Atkinson et al., 2014). Additionally, obesity, sedentary lifestyle, unhealthy diet, smoking, stress, and urbanization significantly contribute to the development of type 2 diabetes mellitus by promoting insulin resistance and metabolic dysfunction. Thus, the interaction between genetic susceptibility and environmental influences ultimately determines the onset and progression of diabetes mellitus.

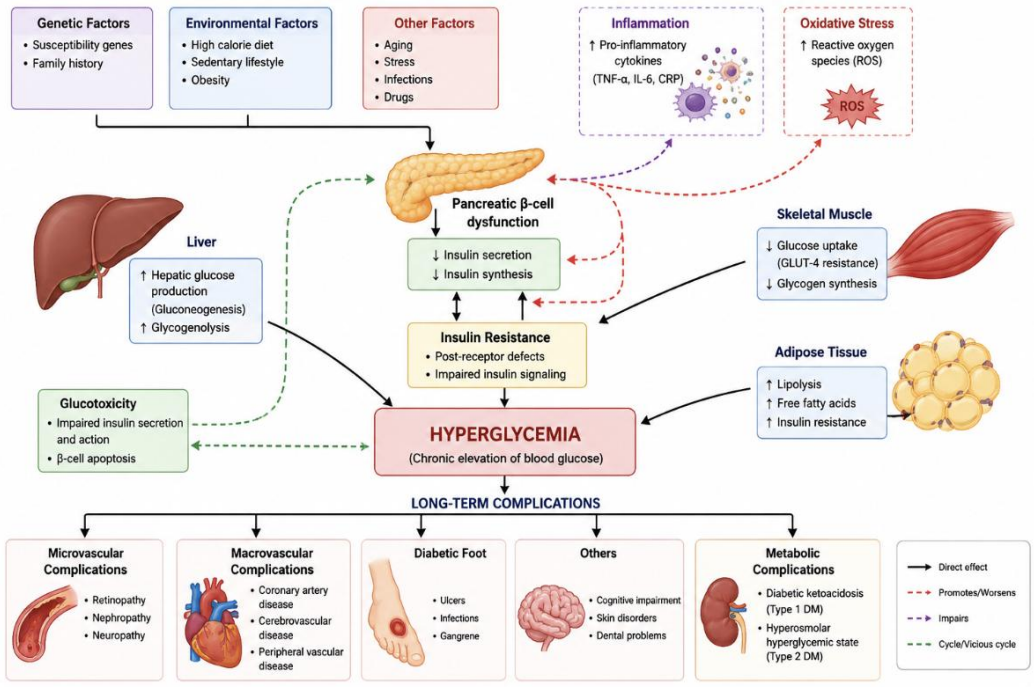

Figure 1. Pathophysiology of Diabetes Mellitus

3. Classification of Diabetes Mellitus

Diabetes mellitus is a heterogeneous group of metabolic disorders characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The classification of diabetes mellitus is primarily based on etiology and pathophysiological mechanisms. According to the classification proposed by the American Diabetes Association, diabetes mellitus is broadly categorized into type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes mellitus, and other specific types of diabetes (American Diabetes Association, 2024). Proper classification is essential for accurate diagnosis, treatment selection, and prevention of disease-related complications.

3.1 Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder characterized by destruction of pancreatic β-cells, resulting in absolute insulin deficiency. It commonly occurs during childhood or adolescence, although it may develop at any age. Genetic susceptibility and environmental factors such as viral infections are considered important contributors to autoimmune β-cell destruction (Atkinson et al., 2014). Patients with T1DM typically present with symptoms including polyuria, polydipsia, polyphagia, weight loss, fatigue, and blurred vision. Due to the absence of endogenous insulin, patients are at high risk of developing diabetic ketoacidosis, a serious acute complication. The presence of autoantibodies such as glutamic acid decarboxylase antibodies and islet cell antibodies aids in diagnosis (DiMeglio et al., 2018). Management primarily involves lifelong insulin therapy, regular blood glucose monitoring, dietary regulation, and lifestyle modifications. Recent advances in continuous glucose monitoring and insulin pump technologies have further improved glycemic control and quality of life in T1DM patients.

3.2 Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and is characterized by insulin resistance along with progressive β-cell dysfunction. It is strongly associated with obesity, sedentary lifestyle, unhealthy diet, aging, and genetic factors (DeFronzo et al., 2015). The disease develops gradually, and common symptoms include excessive thirst, frequent urination, fatigue, blurred vision, and delayed wound healing. Chronic hyperglycemia may lead to complications such as nephropathy, neuropathy, retinopathy, and cardiovascular disease. Management involves lifestyle modification, oral antidiabetic drugs, insulin therapy, and newer agents such as GLP-1 receptor agonists and SGLT2 inhibitors, which also provide cardiovascular and renal benefits (Davies et al., 2022).

3.3 Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is a condition characterized by glucose intolerance first identified during pregnancy, usually during the second or third trimester. It develops due to increased insulin resistance caused by hormonal changes during pregnancy (Plows et al., 2018). Risk factors include obesity, advanced maternal age, family history of diabetes, and previous gestational diabetes. Uncontrolled GDM may lead to complications such as preeclampsia, cesarean delivery, macrosomia, and neonatal hypoglycemia. Proper management through dietary control, exercise, blood glucose monitoring, and insulin therapy when required is essential to reduce maternal and fetal complications.

3.4 Other Specific Types of Diabetes

Other specific types of diabetes include less common forms caused by genetic defects, pancreatic diseases, endocrine disorders, infections, or certain medications. Monogenic diabetes such as maturity-onset diabetes of the young (MODY) results from genetic mutations affecting β-cell function and insulin secretion (Tattersall, 2005). Diseases of the exocrine pancreas including pancreatitis and pancreatic cancer may also cause secondary diabetes. Endocrine disorders such as Cushing's syndrome and hyperthyroidism can induce hyperglycemia through hormonal imbalance. In addition, prolonged use of glucocorticoids, antipsychotics, and immunosuppressive drugs may lead to drug-induced diabetes. Identification of the underlying cause is important because management strategies may differ from conventional type 1 or type 2 diabetes mellitus.

Table 1: Classification of Diabetes Mellitus

Type of Diabetes	Main Cause	Key Characteristics	Common Treatment Approaches
Type 1 Diabetes Mellitus	Autoimmune destruction of pancreatic β-cells	Absolute insulin deficiency, usually early onset	Insulin therapy, glucose monitoring
Type 2 Diabetes Mellitus	Insulin resistance with β-cell dysfunction	Most common form, associated with obesity and sedentary lifestyle	Lifestyle modification, oral antidiabetic drugs, insulin
Gestational Diabetes Mellitus	Hormonal changes during pregnancy causing insulin resistance	Develops during pregnancy, increases maternal and fetal risks	Dietary management, exercise, insulin if required
Other Specific Types	Genetic defects, pancreatic diseases, endocrine disorders, drug-induced diabetes	Less common and variable presentation	Cause-specific management

4. Clinical Manifestations and Complications

Diabetes mellitus presents with a wide range of clinical manifestations resulting from chronic hyperglycemia and metabolic disturbances. The severity and progression of symptoms vary depending on the type of diabetes, duration of disease, and level of glycemic control. Persistent hyperglycemia can lead to acute metabolic emergencies as well as long-term microvascular and macrovascular complications affecting multiple organ systems (Forbes & Cooper, 2013).

4.1 Common Clinical Symptoms

The common clinical manifestations of diabetes mellitus include polyuria, polydipsia, polyphagia, unexplained weight loss, fatigue, and blurred vision. Elevated blood glucose levels cause osmotic diuresis, leading to excessive urination and increased thirst (American Diabetes Association, 2024). Patients may also experience recurrent infections, delayed wound healing, dry skin, weakness, and numbness or tingling in the extremities. In type 1 diabetes mellitus, symptoms usually appear rapidly, whereas type 2 diabetes mellitus often develops gradually and may remain undiagnosed until complications occur.

4.2 Acute Complications

Acute complications of diabetes mellitus are serious metabolic emergencies that include diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), and hypoglycemia. DKA commonly occurs in type 1 diabetes mellitus due to absolute insulin deficiency, leading to hyperglycemia, ketosis, and metabolic acidosis. Symptoms include nausea, vomiting, dehydration, abdominal pain, and altered consciousness (Kitabchi et al., 2009). HHS is more common in type 2 diabetes mellitus and is characterized by severe hyperglycemia, hyperosmolarity, and profound dehydration without significant ketosis. Hypoglycemia may occur due to excessive insulin administration, missed meals, or strenuous exercise and presents with sweating, tremors, dizziness, confusion, and, in severe cases, seizures or loss of consciousness. Immediate medical management is essential to prevent life-threatening complications.

4.3 Chronic Complications

Chronic complications of diabetes mellitus develop due to prolonged hyperglycemia and are primarily categorized into microvascular and macrovascular complications. These complications significantly contribute to morbidity, mortality, and reduced quality of life among diabetic patients.

4.3.1 Diabetic Neuropathy

Diabetic neuropathy is a common microvascular complication of diabetes mellitus caused by chronic hyperglycemia-induced nerve damage. Persistent high blood glucose levels lead to oxidative stress, microvascular injury, and metabolic disturbances that impair nerve function (Feldman et al., 2019). Peripheral neuropathy is the most frequent form and presents with numbness, tingling, burning sensation, pain, and loss of sensation, especially in the feet and hands. Autonomic neuropathy may affect cardiovascular, gastrointestinal, and genitourinary systems, causing symptoms such as orthostatic hypotension, gastroparesis, and bladder dysfunction. If untreated, diabetic neuropathy may increase the risk of foot ulcers, infections, and lower-limb amputations. Early diagnosis and proper glycemic control are important to prevent disease progression and complications.

4.3.2 Diabetic Nephropathy

Diabetic nephropathy is a progressive kidney disorder caused by long-term hyperglycemia and is a major cause of chronic kidney disease and end-stage renal failure. Persistent high blood glucose levels lead to glomerular hyperfiltration, thickening of the glomerular basement membrane, and renal fibrosis (Alicic et al., 2017). The earliest sign is microalbuminuria, which may progress to macroalbuminuria and reduced kidney function. Patients may also develop hypertension, edema, and renal insufficiency. Early screening and proper control of blood glucose and blood pressure are essential to slow disease progression. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are commonly used for renal protection.

4.3.3 Diabetic Retinopathy

Diabetic retinopathy is a major microvascular complication of diabetes mellitus and a leading cause of preventable blindness. Chronic hyperglycemia damages retinal blood vessels, causing increased vascular permeability, ischemia, and abnormal neovascularization (Cheung et al., 2010). It is classified into non-proliferative and proliferative diabetic retinopathy. Early stages are often asymptomatic, but disease progression may lead to blurred vision, retinal hemorrhage, floaters, and vision loss. Macular edema is another serious complication affecting visual acuity. Regular eye examinations and strict glycemic control are essential for early detection and prevention, while advanced cases may require laser therapy, anti-VEGF treatment, or surgical intervention.

4.3.4 Cardiovascular Complications

Cardiovascular complications are the leading cause of mortality in patients with diabetes mellitus. Chronic hyperglycemia, hypertension, dyslipidemia, endothelial dysfunction, and

inflammation contribute to accelerated atherosclerosis and vascular damage (Low Wang et al., 2016). Diabetic patients are at increased risk of coronary artery disease, myocardial infarction, stroke, peripheral arterial disease, and heart failure. Insulin resistance and associated metabolic abnormalities further increase cardiovascular risk. Prevention strategies include proper glycemic control, blood pressure and lipid management, healthy diet, physical activity, and smoking cessation. Newer antidiabetic agents such as SGLT2 inhibitors and GLP-1 receptor agonists have also shown significant cardiovascular protective effects.

Table 2. Chronic Complications of Diabetes Mellitus

Complication	Affected Organ/System	Major Clinical Features
Diabetic Neuropathy	Nervous system	Numbness, tingling, pain, loss of sensation
Diabetic Nephropathy	Kidneys	Proteinuria, reduced renal function, kidney failure
Diabetic Retinopathy	Eyes	Vision impairment, retinal damage, blindness
Cardiovascular Disease	Heart and blood vessels	Hypertension, coronary artery disease, stroke
Diabetic Foot Ulcers	Peripheral circulation and nerves	Poor wound healing, infections, amputation risk

5. Diagnosis of Diabetes Mellitus

The diagnosis of diabetes mellitus is essential for early therapeutic intervention, prevention of complications, and long-term disease management. Diabetes is diagnosed primarily through biochemical assessment of blood glucose levels and glycated hemoglobin. Because chronic hyperglycemia may remain asymptomatic for several years, especially in type 2 diabetes mellitus, standardized diagnostic criteria and screening programs play a major role in reducing disease burden and associated morbidity (Petersmann et al., 2019).

5.1 Diagnostic Criteria

The diagnosis of diabetes mellitus is based on established biochemical criteria including fasting plasma glucose ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test, HbA1c ≥6.5%, or random plasma glucose ≥200 mg/dL in symptomatic individuals (World Health Organization, 2019). Prediabetes represents an intermediate state of impaired glucose regulation and is associated with an increased risk of developing type 2 diabetes mellitus and cardiovascular disease (Buysschaert & Bergman, 2011). Early identification of high-risk individuals allows implementation of preventive measures such as lifestyle modification, weight management, and physical activity. In asymptomatic individuals, repeat testing is generally recommended to confirm the diagnosis due to possible biological and laboratory variations.

5.2 Blood Glucose Tests

Blood glucose testing is essential for the diagnosis and monitoring of diabetes mellitus. Fasting plasma glucose (FPG) testing is widely used because it is simple, economical, and reliable for assessing basal glucose regulation (Sacks, 2011). The oral glucose tolerance test (OGTT) is more sensitive for detecting impaired glucose tolerance and early diabetes and is especially useful in gestational diabetes mellitus (Hostalek, 2019). Random blood glucose testing is commonly performed in symptomatic individuals presenting with classical features of hyperglycemia. In recent years, continuous glucose monitoring (CGM) systems have improved diabetes management by providing real-time glucose measurements, better glycemic profiling, and reduced risk of hypoglycemia, particularly in insulin-treated patients (Battelino et al., 2019).

5.3 HbA1c Testing

Glycated hemoglobin (HbA1c) testing is an important tool for the diagnosis and monitoring of diabetes mellitus because it reflects average blood glucose levels over the previous 8–12 weeks (Selvin, 2016). HbA1c is formed through non-enzymatic glycation of hemoglobin and provides an assessment of long-term glycemic control. It offers several advantages including convenience, minimal day-to-day variability, and no requirement for fasting. Elevated HbA1c levels are strongly associated with an increased risk of diabetic complications such as retinopathy, nephropathy, neuropathy, and cardiovascular disease (Little & Sacks, 2018). However, conditions affecting red blood cell lifespan, including anemia, hemoglobinopathies, and chronic kidney disease, may interfere with HbA1c accuracy, making plasma glucose-based tests important complementary diagnostic methods.

5.4 Screening and Early Detection

Screening and early detection are essential for the prevention and management of diabetes mellitus, particularly because many individuals with type 2 diabetes remain undiagnosed for years (NCD Risk Factor Collaboration, 2016). Screening is recommended for high-risk individuals such as those with obesity, family history of diabetes, hypertension, sedentary lifestyle, polycystic ovary syndrome, or previous gestational diabetes mellitus. Common screening methods include fasting plasma glucose, HbA1c testing, and oral glucose tolerance tests. Early lifestyle interventions including weight management, healthy diet, regular physical activity, and smoking cessation can significantly reduce the risk of progression from prediabetes to diabetes mellitus (Knowler et al., 2002). Furthermore, advances in digital healthcare technologies and artificial intelligence are improving early diagnosis and personalized risk assessment.

6. Current Treatment Approaches

The management of diabetes mellitus primarily aims to achieve optimal glycemic control, prevent complications, and improve patient quality of life. Current treatment strategies include lifestyle modification, insulin therapy, oral antidiabetic drugs, and combination therapy. Treatment selection depends on the type of diabetes, disease severity, comorbidities, and individual patient characteristics (Inzucchi et al., 2015).

6.1 Lifestyle and Dietary Management

Lifestyle modification is the foundation of diabetes management and includes dietary regulation, physical activity, weight management, smoking cessation, and behavioral counseling. Balanced diets rich in whole grains, fruits, vegetables, and dietary fiber help improve glycemic control and lipid metabolism, while regular physical activity enhances insulin sensitivity and glucose utilization (Franz et al., 2017). Weight reduction is particularly beneficial in patients with type 2 diabetes mellitus and obesity. Several studies have demonstrated that intensive lifestyle interventions can delay or prevent progression from prediabetes to diabetes mellitus.

6.2 Insulin Therapy

Insulin therapy is essential for type 1 diabetes mellitus and may also be required in advanced type 2 diabetes mellitus. Insulin preparations are classified as rapid-acting, short-acting, intermediate-acting, and long-acting formulations based on their pharmacokinetic properties (Home, 2021). Basal insulin maintains background glucose control, while prandial insulin regulates postprandial glucose levels. Advances in insulin analogs, insulin pumps, and continuous glucose monitoring systems have improved glycemic management and reduced hypoglycemia risk. However, insulin therapy may still cause hypoglycemia, weight gain, and adherence-related challenges.

6.3 Oral Antidiabetic Drugs

Oral antidiabetic drugs are mainly used in type 2 diabetes mellitus and act through different mechanisms to lower blood glucose levels. Metformin is considered the first-line therapy because it reduces hepatic glucose production and improves insulin sensitivity (Rena et al., 2017). Sulfonylureas stimulate insulin secretion, while thiazolidinediones enhance peripheral insulin sensitivity. DPP-4 inhibitors and GLP-1 receptor agonists improve incretin activity and insulin release, whereas SGLT2 inhibitors reduce glucose reabsorption in the kidneys and additionally provide cardiovascular and renal benefits (McGuire et al., 2021). Drug selection is individualized according to patient condition and therapeutic goals.

6.4 Combination Therapy

Combination therapy is often used when monotherapy fails to achieve adequate glycemic control. Combining drugs with complementary mechanisms of action provides better glucose regulation and may help preserve pancreatic β-cell function (Turner et al., 1999). Common combinations include metformin with sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or insulin. Although combination therapy improves therapeutic outcomes, careful monitoring is necessary to minimize adverse effects, drug interactions, and treatment burden.

Table 3. Major Classes of Antidiabetic Drugs and Their Mechanisms

Drug Class	Example	Mechanism of Action	Major Benefits
Biguanides	Metformin	Reduces hepatic glucose production and improves insulin sensitivity	First-line therapy, weight neutral
Sulfonylureas	Glimepiride, Glibenclamide	Stimulate pancreatic insulin secretion	Effective glucose lowering
Thiazolidinediones	Pioglitazone	Improve peripheral insulin sensitivity	Better insulin utilization
DPP-4 Inhibitors	Sitagliptin, Vildagliptin	Increase incretin hormone activity	Low risk of hypoglycemia
GLP-1 Receptor Agonists	Liraglutide, Semaglutide	Enhance insulin secretion and reduce appetite	Weight loss, cardiovascular benefits
SGLT2 Inhibitors	Dapagliflozin, Empagliflozin	Increase urinary glucose excretion	Cardiovascular and renal protection
Insulin Preparations	Insulin glargine, insulin lispro	Replace or supplement endogenous insulin	Essential in Type 1 diabetes

7. New and Emerging Treatment Approaches

Recent advances in diabetes research have led to the development of innovative therapeutic strategies aimed at improving glycemic control, reducing complications, and targeting the underlying pathophysiology of the disease. Emerging approaches including advanced pharmacological agents, regenerative medicine, nanotechnology, artificial intelligence, and precision medicine are transforming diabetes management and improving patient outcomes (Rodriguez-Gutierrez & McCoy, 2019).

7.1 GLP-1 Receptor Agonists and SGLT2 Inhibitors

GLP-1 receptor agonists and SGLT2 inhibitors represent important advances in the treatment of type 2 diabetes mellitus. GLP-1 receptor agonists enhance glucose-dependent insulin secretion, suppress glucagon release, delay gastric emptying, and promote weight loss (Müller et al., 2019). SGLT2 inhibitors lower blood glucose by increasing urinary glucose

excretion and additionally provide cardiovascular and renal protective effects (Heerspink et al., 2020). Although highly effective, these agents may cause gastrointestinal disturbances, urinary tract infections, and rare cases of diabetic ketoacidosis.

7.2 Stem Cell Therapy

Stem cell therapy is a promising regenerative approach aimed at restoring pancreatic β-cell function and insulin production. Various stem cell sources including embryonic stem cells, induced pluripotent stem cells, and mesenchymal stem cells are being investigated for diabetes treatment (Shapiro et al., 2017). These therapies may help regenerate damaged pancreatic tissue and modulate immune responses. However, challenges such as immune rejection, ethical concerns, tumorigenicity, and long-term safety still limit widespread clinical application.

7.3 Gene Therapy

Gene therapy focuses on correcting genetic and molecular abnormalities associated with diabetes mellitus. Techniques involving viral vectors and gene-editing tools such as CRISPR-Cas9 are being explored to improve insulin production, enhance insulin sensitivity, and protect pancreatic β-cells (Riu et al., 2016). Although experimental studies have shown promising results, concerns regarding safety, delivery efficiency, and immune reactions remain important barriers to clinical translation.

7.4 Nanotechnology-Based Drug Delivery

Nanotechnology-based drug delivery systems improve drug stability, bioavailability, controlled release, and targeted delivery of antidiabetic agents. Nanocarriers such as nanoparticles, liposomes, and nanoemulsions are being investigated for oral insulin delivery and glucose-responsive insulin release (Veiseh et al., 2015). Nanotechnology may also improve glucose monitoring and reduce systemic side effects; however, issues related to nanotoxicity and regulatory approval remain challenging.

7.5 Artificial Pancreas Systems

Artificial pancreas systems combine continuous glucose monitoring devices, insulin pumps, and automated algorithms to mimic physiological insulin regulation (Boughton & Hovorka, 2021). These systems continuously monitor glucose levels and automatically adjust insulin delivery, improving glycemic control and reducing hypoglycemia risk. Despite significant benefits, high cost, technical complexity, and device-related limitations continue to affect accessibility.

7.6 Personalized and Precision Medicine

Personalized and precision medicine approaches aim to tailor diabetes treatment according to an individual's genetic profile, metabolic status, and disease characteristics. Advances in genomics, metabolomics, artificial intelligence, and wearable technologies are improving individualized therapeutic strategies and predictive disease management (Pearson, 2019). Although precision medicine offers significant future potential, challenges including cost, accessibility, and data privacy concerns still need to be addressed.

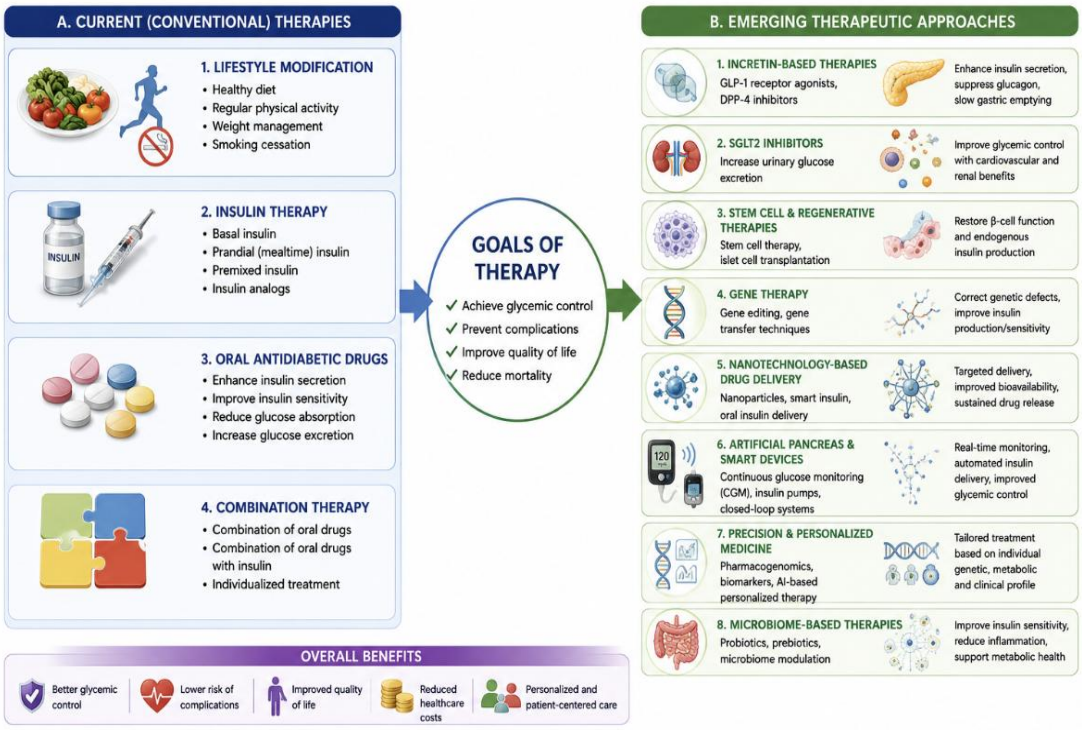

Figure 2. Current and Emerging Therapeutic Approaches for Diabetes Mellitus

8. Herbal and Natural Therapeutics

Herbal and natural therapeutics have gained significant attention in the management of diabetes mellitus due to their potential efficacy, reduced side effects, affordability, and long history of traditional use. Various medicinal plants and phytochemicals exhibit antihyperglycemic, antioxidant, anti-inflammatory, and insulin-sensitizing properties that help regulate glucose metabolism and prevent diabetic complications. Traditional systems such as Ayurveda, Traditional Chinese Medicine, and Unani medicine have long employed herbal remedies for diabetes management (Yatoo et al., 2017).

Natural therapeutics may act through multiple mechanisms, including stimulation of insulin secretion, enhancement of glucose uptake, inhibition of carbohydrate digestion, reduction of oxidative stress, and protection of pancreatic β-cells. Growing scientific interest has led to extensive investigation of plant-derived compounds as complementary or alternative options for diabetes management.

8.1 Antidiabetic Medicinal Plants

Several medicinal plants have shown significant antidiabetic activity in experimental and clinical studies, including *Momordica charantia*, *Trigonella foenum-graecum*, *Gymnema sylvestre*, *Azadirachta indica*, and *Curcuma longa*.

Momordica charantia contains charantin, vicine, and polypeptide-p, which exhibit insulin-like activity and improve glucose utilization, while also enhancing insulin secretion and reducing intestinal glucose absorption (Joseph & Jini, 2013). *Trigonella foenum-graecum* seeds, rich in soluble fiber and 4-hydroxyisoleucine, improve insulin secretion and sensitivity, with beneficial effects on blood glucose and lipid profiles.

Gymnema sylvestre supports diabetes management through gymnemic acids that may promote β-cell regeneration and reduce glucose absorption. *Azadirachta indica* exhibits antihyperglycemic and antioxidant effects, while *Curcuma longa* (curcumin) improves insulin sensitivity and reduces inflammation and diabetic complications.

8.2 Bioactive Phytoconstituents

Bioactive phytoconstituents such as flavonoids, alkaloids, terpenoids, glycosides, polyphenols, saponins, and tannins play a key role in antidiabetic activity (Patel et al., 2012). Flavonoids like quercetin and kaempferol protect β-cells from oxidative stress and improve insulin signaling. Alkaloids such as berberine activate AMP-activated protein kinase (AMPK), enhancing insulin sensitivity and reducing hepatic glucose production.

Other compounds such as curcumin, resveratrol, genistein, and epigallocatechin gallate regulate glucose homeostasis, lipid metabolism, oxidative stress, and inflammation, making them promising candidates for novel antidiabetic therapies and nutraceutical development.

8.3 Challenges in Herbal Therapy

Despite their therapeutic potential, herbal therapies face several limitations. Lack of standardization due to variability in plant source, extraction methods, and phytochemical composition affects consistency and efficacy (Ekor, 2014). Limited clinical evidence, along with insufficient large-scale randomized controlled trials, restricts their integration into mainstream medicine.

Additional concerns include herb–drug interactions, poor bioavailability, contamination, and lack of regulatory control. Therefore, further scientific validation, standardization, and clinical evaluation are necessary to ensure the safety and reliability of herbal antidiabetic therapies.

9. Future Perspectives and Recent Advances

Recent advances in biomedical research and digital technologies have significantly improved diabetes management. Emerging strategies are focused on early diagnosis, personalized treatment, β-cell preservation, and prevention of long-term complications. Innovative approaches such as regenerative medicine, artificial intelligence, nanotechnology, and gene-editing technologies are expected to enhance therapeutic outcomes and patient quality of life (ElSayed et al., 2023).

Immunotherapy and stem cell-based therapies have shown promising potential in restoring pancreatic β-cell function and delaying disease progression, particularly in type 1 diabetes mellitus. Monoclonal antibodies such as teplizumab may delay autoimmune β-cell destruction in high-risk individuals (Herold et al., 2019). Artificial intelligence integrated with continuous glucose monitoring systems and insulin pumps is also improving real-time glucose management and treatment precision (Contreras & Vehi, 2018).

Nanotechnology-based drug delivery systems, glucose-responsive insulin formulations, and implantable biosensors are being investigated to improve insulin delivery and glycemic control. In addition, precision medicine using genomic and biomarker-based approaches may allow individualized therapy according to patient-specific characteristics and drug responses (Udler et al., 2019).

Recent studies on gut microbiota have further highlighted its role in glucose metabolism and insulin resistance, suggesting potential therapeutic applications through microbiome modulation. Although these innovations show considerable promise, challenges such as high cost, safety concerns, and limited accessibility must be addressed before widespread clinical implementation.

10. Conclusion

Diabetes mellitus is a multifactorial metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both, and is associated with serious microvascular and macrovascular complications. The growing global prevalence of diabetes emphasizes the importance of early diagnosis, effective glycemic control, and comprehensive management strategies. Conventional treatments including lifestyle modification, insulin therapy, and oral antidiabetic drugs remain fundamental in disease management, while newer approaches such as GLP-1 receptor agonists, SGLT2 inhibitors, stem cell therapy, gene therapy, nanotechnology-based delivery systems, and artificial pancreas technologies have shown significant therapeutic potential. Additionally, herbal and natural therapeutics continue to gain attention due to their beneficial pharmacological properties. Advances in precision medicine, artificial intelligence, and

regenerative therapies are expected to further improve individualized diabetes care and clinical outcomes. Nevertheless, challenges related to safety, cost, accessibility, and long-term efficacy still require extensive research and clinical validation for effective global diabetes management.

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12. Conflict of Interest

The authors declare that there are no conflicts of interest.

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