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Diabetes Mellitus: A Comprehensive Review of Types, Pathophysiology, Complications, and Standards of Care in Diabetes 2025

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Abstract

Diabetes mellitus represents a complex spectrum of metabolic disorders with diverse pathophysiological mechanisms unified by the common endpoint of hyperglycemia. The classification into different types—primarily type 1, type 2, gestational, and various rare forms—reflects the heterogeneity of the disease and necessitates tailored approaches to diagnosis and management. The pathophysiology of diabetes involves intricate interactions between insulin secretion and action, with distinct mechanisms leading to beta cell destruction in type 1 diabetes and the dual defects of insulin resistance and progressive beta cell dysfunction in type 2 diabetes. The complications of diabetes demonstrate the profound impact of chronic hyperglycemia on multiple organ systems through both microvascular and macrovascular damage. The selective vulnerability of certain cell types to hyperglycemia-induced injury explains the pattern of complications affecting the kidneys, eyes, nerves, and cardiovascular system. Understanding the unifying mechanisms and specific metabolic pathways involved in these complications has facilitated the development of targeted preventive and therapeutic strategies.

Recent updates from the 2025 Standards of Care in Diabetes reflect the evolving understanding of the disease and its management, with increasing emphasis on technological solutions, individualized approaches, and comprehensive risk reduction. The reconceptualization of diabetes as part of a broader metabolic dysfunction syndrome represents an important paradigm shift that may lead to more integrated approaches to prevention and treatment. Moving forward, continued research into the pathophysiological mechanisms of diabetes and its complications will be essential for developing novel therapeutic targets and improving outcomes for the growing number of individuals affected by this global health challenge.

Keywords: Diabetes mellitus, insulin, hyperglycemia, 2025 Standards of Care in Diabetes.

Introduction:

Diabetes mellitus represents a complex group of metabolic disorders characterized by chronic hyperglycemia. This condition results from defects in insulin secretion, insulin action, or a combination of both factors (1,2). It is estimated that 537 million people worldwide had diabetes in 2020; by 2030, this would have risen to 552 million. The number of people with type 2 DM is increasing in every country, with 80% of people with DM living in low- and middle-income countries. DM caused 4.6 million deaths in 2011 (3,4).

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Genetic predisposition plays a significant role, and environmental triggers, such as viral infections, may also contribute to its development. While genetics predispose some individuals to diabetes, lifestyle modifications, such as maintaining a healthy weight, engaging in regular physical activity, and adopting a balanced diet, are crucial in preventing and managing this chronic disease. Early diagnosis and appropriate medical care are essential to mitigate its complications and improve the quality of life for those affected (5,6).

The disease manifests in several forms, each with distinct pathophysiological mechanisms, while sharing common complications that significantly impact patient quality of life and survival. This review synthesizes current understanding of diabetes mellitus types, underlying pathophysiological processes, and associated complications, incorporating recent updates from the 2025 Standards of Care in Diabetes.

1. Types of Diabetes Mellitus:

A. Type 1 Diabetes:

Type 1 diabetes is characterized by autoimmune destruction of the pancreatic beta cells, resulting in absolute insulin deficiency. According to the American Diabetes Association, type 1 diabetes occurs when "blood glucose (sugar) level is too high because your body can't make a hormone called insulin" (7). This autoimmune process attacks the insulin-producing cells in the pancreas, leading to a complete inability to produce insulin. The physiological consequence is straightforward but severe: glucose from carbohydrate metabolism enters the bloodstream but cannot be transported into cells for energy utilization. Consequently, glucose accumulates in the bloodstream, causing hyperglycemia and triggering the classic symptoms of polyuria, polydipsia, and polyphagia, often accompanied by unexplained weight loss despite increased appetite (7,8).

Type 2 Diabetes

Type 2 diabetes, the most prevalent form globally, presents a more complex pathophysiological picture involving both insulin resistance and progressive beta cell dysfunction. According to research, "Type 2 diabetes is characterized by a combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells" (9). Unlike type 1 diabetes, insulin production continues but becomes increasingly ineffective at controlling blood glucose levels. The disease typically develops gradually, often preceded by a prediabetic state characterized by impaired glucose tolerance or impaired fasting glucose. Type 2 diabetes has been increasingly recognized as "one component of metabolic syndrome" or what some researchers term "metabolic dysfunction syndrome (MDS)" (7,9).

B. Gestational Diabetes

Gestational diabetes develops during pregnancy and typically resolves following delivery, though it significantly increases the risk of developing type 2 diabetes later in life. This form of diabetes results from pregnancy-induced insulin resistance combined with inadequate compensatory insulin secretion. Hormonal changes during pregnancy, particularly in the second and third trimesters, contribute to insulin resistance as the body attempts to prioritize nutrient delivery to the developing fetus. Gestational diabetes requires careful management to prevent complications affecting both mother and child, including macrosomia, birth trauma, and neonatal hypoglycemia (7,10).

D. Other Types of Diabetes:

Beyond the common classifications, approximately 2% of diabetes cases fall into other categories with distinct etiologies. These include monogenic forms such as Maturity Onset Diabetes of the Young (MODY) and neonatal diabetes, which result from single-gene mutations affecting pancreatic beta cell function or insulin action. Other specific types include Latent Autoimmune Diabetes in Adults

(LADA), which shares features of both type 1 and type 2 diabetes, and secondary diabetes arising from conditions like cystic fibrosis, pancreatic disease, or medication effects (particularly steroids and antipsychotics). Rare genetic syndromes such as Wolfram Syndrome and Alström Syndrome also include diabetes as a prominent feature (11).

Pathophysiology of Diabetes Mellitus:

1.1. General Metabolic Dysregulation:

Diabetes pathophysiology centers around disrupted glucose homeostasis, with different types sharing the endpoint of hyperglycemia while arising through distinct mechanisms. The maintenance of normal blood glucose levels depends on a complex interplay between insulin secretion from pancreatic beta cells and insulin sensitivity in peripheral tissues, particularly muscle, liver, and adipose tissue. When this balance is disturbed—whether through autoimmune destruction of beta cells, progressive beta cell dysfunction, insulin resistance, or other mechanisms—hyperglycemia results. Chronic hyperglycemia triggers a cascade of metabolic abnormalities through multiple pathways, including "inflammation, endoplasmic reticulum stress (ERS), oxidative stress, and ectopic lipid deposition" (2,7).

1.2. Type 1 Diabetes Pathophysiology:

In type 1 diabetes, an autoimmune process targets and destroys the insulin-producing beta cells in the pancreatic islets. Genetic susceptibility combined with environmental triggers initiates this autoimmune response, which may progress over months or years before clinical symptoms emerge. As beta cell mass declines, insulin production becomes increasingly inadequate. When approximately 80-90% of beta cells are destroyed, the remaining insulin-producing capacity becomes insufficient to maintain glucose homeostasis. At this point, the body continues to break down carbohydrates into glucose, but without adequate insulin, this glucose cannot enter cells, instead accumulating in the bloodstream and leads to hyperglycemia (12).

Type 2 Diabetes Pathophysiology:

The pathophysiology of type 2 diabetes is multifactorial and progressive, involving two primary defects: insulin resistance and inadequate insulin secretion. Research indicates that "for type 2 diabetes mellitus to occur, both insulin resistance and inadequate insulin secretion must exist." Insulin resistance typically precedes the development of hyperglycemia, often by many years. During this period, pancreatic beta cells compensate by increasing insulin secretion, maintaining relatively normal glucose levels despite reduced tissue sensitivity. However, this compensatory mechanism eventually fails as beta cells become dysfunctional and begin to decline in mass (13).

A critical aspect of type 2 diabetes pathophysiology involves what has been described as an "islet paracrinopathy in which the reciprocal relationship between the glucagon-secreting alpha cell and the insulin-secreting beta cell is lost, leading to hyperglucagonemia and hence the consequent hyperglycemia". This derangement in alpha cell function results in inappropriate glucagon secretion, exacerbating hyperglycemia through increased hepatic glucose production. With disease progression, pancreatic atrophy may occur, further compromising both endocrine and exocrine pancreatic functions (13,14).

2. Mechanisms of Diabetic Complications:

2.1. Unifying Mechanism of Tissue Damage:

The DCCT (Diabetes Control and Complications Trial) and UKPDS (U.K. Prospective Diabetes Study) established that hyperglycemia initiates the tissue damage observed in diabetic complications. While genetic factors and comorbidities like hypertension modify this process, hyperglycemia remains the primary driver. Interestingly, not all tissues are equally susceptible to hyperglycemia-induced damage. Research has revealed that "cells damaged by hyperglycemia are those that cannot do this efficiently"—specifically, cells that cannot

effectively reduce glucose transport into the cell when exposed to hyperglycemic conditions. This explains why damage occurs selectively in capillary endothelial cells in the retina, mesangial cells in the renal glomerulus, and neurons and Schwann cells in peripheral nerves, as these cell types maintain high intracellular glucose concentrations during hyperglycemia (15).

Metabolic Pathways in Complications:

Hyperglycemia induces tissue damage through several interconnected biochemical pathways. These include the polyol pathway, hexosamine biosynthetic pathway, protein kinase C activation, and increased formation of advanced glycation end-products (AGEs). In the polyol pathway, excess glucose is converted to sorbitol and subsequently to fructose, depleting NADPH and glutathione, thereby increasing oxidative stress. The hexosamine pathway diverts excess glucose metabolism to produce N-acetylglucosamine, which modifies transcription factors and alters gene expression. Protein kinase C activation affects vascular permeability and blood flow, while AGEs crosslink proteins, disrupting their normal function and triggering inflammatory responses. These pathways converge to produce reactive oxygen species, creating a cycle of oxidative stress that perpetuates tissue damage even after hyperglycemia is controlled (16).

3. Diabetic Complications:

3.1. Microvascular Complications:

Nephropathy:

Diabetic nephropathy represents the leading cause of end-stage renal disease in Western countries, developing in approximately 20-40% of patients with diabetes. Poor glycemic control significantly increases the risk of nephropathy development. The condition progresses from microalbuminuria to overt proteinuria and eventually to declining glomerular filtration rate if left untreated. Clinically, nephropathy manifests as "an emergence of proteinuria with a concomitant reduction in glomerular filtration rate, leading to fatal uremia if not treated". The development of hypertension frequently accompanies diabetic nephropathy, creating a vicious cycle that accelerates kidney damage. Beyond renal failure, diabetic nephropathy also increases the risk of macrovascular complications, including strokes and myocardial infarctions, making it a significant predictor of overall mortality in patients with diabetes (16.17).

Retinopathy:

Diabetic retinopathy stands as the leading cause of blindness in working-age adults (20-74 years), with virtually all patients with type 1 diabetes and more than 60% of those with type 2 diabetes developing some degree of retinopathy within 20 years of diagnosis. This complication manifests as a spectrum of lesions affecting the retinal microvasculature, including "vascular permeability changes, capillary degeneration, capillary microaneurysms, and abnormal production of blood vessels". The pathogenesis begins with hyperglycemia-induced alterations in the blood-retinal barrier and increased vascular permeability. As the condition progresses, it may advance from non-proliferative (characterized by microaneurysms, hemorrhages, and hard exudates) to proliferative retinopathy (marked by neovascularization and the risk of vitreous hemorrhage and retinal detachment). Color vision deficiency often accompanies these changes, further impacting quality of life (16,18).

Neuropathy:

Diabetic neuropathy affects more than half of all diabetic patients, making it one of the most common complications of the disease. This complication encompasses a heterogeneous group of disorders affecting different parts of the nervous system, with distal symmetric polyneuropathy being the most prevalent form. Advanced diabetic neuropathy results in impaired nerve fiber function, leading to "a total decline in sensory perception". This sensory loss creates a significant risk for undetected injuries,

particularly in the lower extremities, contributing to the development of diabetic foot ulcers. Additionally, neuropathy may manifest as painful conditions (hyperalgesia and allodynia), autonomic dysfunction affecting cardiovascular, gastrointestinal, and genitourinary systems, and focal mononeuropathies. The comprehensive impact of these neurological disturbances significantly compromises quality of life and increases mortality risk (16,19). **Macrovascular Complications:**

Cardiovascular Disease:

Cardiovascular disease (CVD) represents the leading cause of morbidity and mortality in diabetic patients, accounting for more than half of all deaths related to diabetic complications. The risk profile is so significant that research has shown "the risk of myocardial infarction among diabetic patients was equivalent to normal human subjects with a previous history of myocardial infarction" (16). This striking equivalence has led to diabetes being classified as a coronary heart disease risk equivalent. The spectrum of cardiovascular manifestations includes premature atherosclerosis leading to coronary artery disease, cerebrovascular disease, and peripheral arterial disease. In type 1 diabetes, cardiovascular disease typically develops secondary to diabetic nephropathy, while in type 2 diabetes, both poor glycemic control and kidney disease serve as independent risk factors for cardiovascular complications (20).

Metabolic Complications:

Hyperosmolar Hyperglycemic State:

Hyperosmolar Hyperglycemic State (HHS) represents an acute, life-threatening complication more common in type 2 diabetes, particularly in elderly patients with limited access to water or concurrent illness. This condition develops gradually over days to weeks, typically triggered by an infection combined with dehydration. Physiologically, HHS involves extreme hyperglycemia (often exceeding 600 mg/dL) without significant ketosis, leading to profound osmotic diuresis, dehydration, and mental status changes. Warning signs include excessive urination, extreme thirst, nausea, confusion, drowsiness, and shortness of breath. The mortality rate from HHS remains significantly higher than that of diabetic ketoacidosis, emphasizing the need for prompt recognition and treatment of this medical emergency (21).

Diabetic Ketoacidosis:

Diabetic Ketoacidosis (DKA), while more commonly associated with type 1 diabetes, can occur in any diabetic patient during periods of severe physiological stress. As described in clinical resources, "a lack of insulin can cause harmful substances called ketones to build up in the blood". The pathophysiology involves insulin deficiency combined with counter-regulatory hormone excess (glucagon, catecholamines, cortisol, and growth hormone), leading to increased lipolysis and ketogenesis. The resulting metabolic acidosis, combined with fluid losses from osmotic diuresis, creates a life-threatening situation requiring immediate medical intervention. Clinical manifestations include polyuria, polydipsia, nausea, vomiting, abdominal pain, and in severe cases, Kussmaul respirations and altered mental status (22).

4. Current Management Approaches:

4.1. Standards of Care Updates:

The American Diabetes Association recently released the "Standards of Care in Diabetes—2025," representing the most current evidence-based guidelines for diabetes management. Notable updates include expanded recommendations for continuous glucose monitoring (CGM) use in adults with type 2 diabetes taking glucose-lowering agents other than insulin, reflecting the growing recognition of CGM's value across the diabetes spectrum. The guidelines also address practical challenges like medication shortages, providing "guidance on actions to take during circumstances of medication unavailability" (23). Regarding pharmacotherapy,

the standards offer "additional guidance on the use of GLP-1 receptor agonists beyond weight loss for heart and kidney health benefits" and recommendations for "continuation of weight management pharmacotherapy beyond reaching weight loss goals". Other significant updates include guidance on treating metabolic dysfunction-associated steatotic liver disease, screening for presymptomatic type 1 diabetes, expanded dietary recommendations to support evidence-based eating habits that take into account metabolic objectives, overall caloric intake, and nutritional quality, such as those that include plant-based proteins and fibre.

Guidance on the use of recreational cannabis for type 1 diabetes and those with other forms of diabetes at risk for diabetic ketoacidosis (DKA), Key updates highlighting potentially harmful medications in pregnancy, and guidance for appropriately modifying the care plan (23).

4.2. Prevention and Management Strategies:

While there is currently no cure for diabetes, type 2 diabetes can be prevented or potentially put into remission through targeted interventions (24). Prevention strategies focus on modifiable risk factors, including maintaining a healthy body weight, regular physical activity, balanced nutrition, and smoking cessation. For established diabetes, management approaches have evolved toward more personalized, patient-centered models considering individual factors such as age, comorbidities, preferences, and resources. A holistic approach to diabetes management extends beyond glycemic control to include cardiovascular risk reduction, kidney protection, and prevention of other complications. Regular monitoring for complications through appropriate screenings (eye examinations, kidney function tests, foot examinations) remains essential for early detection and intervention (24).

Because adipocytes produce interleukin 6 (IL-6) and tumour necrosis factor α (TNF-α), which are essential agents for CRP activation, elevated C-reactive protein (CRP) levels have been associated with excess body weight, so it is important to decrease body weight as a diabetic risk factor (25,26).

Diabetes can impair the immune system, leading to a higher susceptibility to infection, and that's why diabetics and immunocompromised patients must go to the medical laboratory for serum ferritin level analysis, to decrease their levels and lower the probability of experiencing serious complications in different viral infections such as COVID-19 (27).

The emerging concept of diabetes as part of a broader metabolic dysfunction syndrome has led some researchers to propose referring to "diabetic complications" as "MDS-related target organ damage (TOD)" to acknowledge that these complications involve not just hyperglycemia but multiple metabolic disturbances (24).

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