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Comprehensive review of diabetes mellitus: Pathophysiology, current management, and emerging therapeutic approaches

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Abstract
Diabetes mellitus (DM), a chronic metabolic disorder marked by hyperglycaemia, results from defects in insulin secretion, insulin action, or both. This comprehensive review examines the pathophysiology of diabetes, highlighting new therapies for DM and other forms of the disease. It outlines current management strategies, including lifestyle modifications, pharmacological interventions, and monitoring techniques aimed at achieving optimal glycaemic control and minimizing complications. Furthermore, it explores emerging therapeutic approaches, such as novel pharmacotherapies, technological advancements in insulin delivery and glucose monitoring, and potential curative strategies like beta-cell replacement and gene therapy. By synthesizing the latest research and clinical guidelines, this review provides a comprehensive overview of diabetes mellitus, aiming to inform and guide healthcare professionals in the effective management and treatment of this prevalent condition.

Keywords: Diabetes mellitus, obesity, diagnosis, current management, and newer drugs

Introduction
Diabetes mellitus (DM) is a chronic, non-communicable metabolic condition that is frequently typified by hyperglycaemia, or elevated blood glucose levels. It is a significant global health problem with increasing prevalence and substantial morbidity and mortality. This review aims to provide a comprehensive understanding of the pathophysiology of diabetes mellitus, discuss current management strategies, and explore emerging therapeutic approaches [1, 2].

In 2021, there were about 536 million adults aged 20 to 79 who had diabetes mellitus (DM); by 2045, this number is expected to increase by 783 million [38]. Globally, the prevalence of type 2 diabetes mellitus (DM), a chronic metabolic condition, has been gradually rising. Due to this trend, the disease is quickly spreading to other parts of the world and is predicted to affect twice as many people in the next ten years as a result of an aging population. This will increase the burden already placed on healthcare providers, particularly in less developed nations. The Cochrane Database of Systemic Reviews, Medline, and citation lists of pertinent papers were searched in order to compile the basis for this review. Type 2 diabetes mellitus, prevalence, current diagnosis, and current therapy are included in the subject heading and key terms [3, 4].

Significance as a Global Health Issue
Morbidity and Mortality: Diabetes is a leading cause of morbidity and premature mortality. It is associated with serious complications, including cardiovascular diseases, neuropathy, nephropathy, retinopathy, and an increased risk of infections.

Economic Burden: The economic impact of diabetes is substantial, encompassing direct medical costs for treatment and indirect costs from loss of productivity, disability, and premature death. Global health expenditures on diabetes were estimated at $966 billion in 2021.

Public Health Challenge: The rising prevalence of diabetes poses significant challenges for healthcare systems worldwide. It requires effective strategies for prevention, early diagnosis, and management to mitigate its impact on individuals and society.

The illness DM can be acute or chronic, and it is frequently linked to many illnesses such as liver disease, kidney dysfunction, and cardiovascular disease. Because untreated diabetes can lead to major complications, early detection of the disease may help prevent disastrous consequences. High blood glucose levels that don't go down, frequent urination, increased thirst, and increased hunger are the main signs of diabetes. As a result, diabetes mellitus is divided into four main groups: Type 1, Type 2, gestational diabetes, and secondary diabetes. For the treatment of diabetes mellitus, there are numerous injectable and oral formulations on the market, including insulin, biguanides, sulphonylureas, etc. The numerous nanotechnologies used in the diagnosis, treatment, and control of diabetes mellitus have received recent attention [5, 6].

2. Pathophysiology of Diabetes Mellitus

The pathophysiology of diabetes mellitus varies between its primary forms, Type 1 and Type 2, but both involve disruptions in glucose metabolism due to problems with insulin. In Type 1 diabetes (T1D), an autoimmune process targets and destroys pancreatic beta cells, which are responsible for producing insulin. This destruction leads to an absolute deficiency of insulin, preventing glucose from entering cells and causing elevated blood glucose levels. Genetic predisposition plays a significant role in T1D, with environmental triggers such as viral infections potentially initiating the autoimmune response [7].

In contrast, Type 2 diabetes (T2D) is characterized by insulin resistance and a progressive decline in pancreatic beta-cell function. Insulin resistance, often associated with obesity, means that cells in the body, particularly muscle, fat, and liver cells, do not respond effectively to insulin. The pancreas compensates by producing more insulin, but over time, beta-cell dysfunction leads to insufficient insulin production relative to the body's needs. T2D has a strong genetic component and is influenced by lifestyle factors such as diet, physical inactivity, and obesity [8, 9].

Other forms of diabetes, including gestational diabetes and monogenic diabetes, have distinct pathophysiological mechanisms. Gestational diabetes occurs due to hormonal changes during pregnancy that induce insulin resistance, while monogenic diabetes results from mutations in a single gene affecting insulin production or action. Despite the differences in their pathophysiology, all forms of diabetes result in chronic hyperglycaemia, which can lead to severe complications such as cardiovascular disease, neuropathy, nephropathy, and retinopathy if not properly managed.

2.1 Causes of Diabetes Mellitus with Emphasis on Obesity as a Key Factor

Diabetes mellitus is a complex disease with various contributing factors. This document outlines the primary causes of diabetes, with a specific focus on obesity, one of the most significant and modifiable risk factors for the development of Type 2 diabetes. It is broadly classified into Type 1, Type 2, and gestational diabetes, with Type 2 diabetes mellitus (T2DM) being the most prevalent form worldwide. The causes of diabetes are multifactorial, involving both genetic and environmental components. While a family history of diabetes, age, ethnicity, and sedentary lifestyle contribute significantly, obesity has emerged as the most prominent and modifiable risk factor, especially in the development of T2DM. Excess body fat, particularly central or abdominal obesity, leads to a cascade of metabolic disturbances including insulin resistance, chronic low-grade inflammation, and lipotoxicity. Adipose tissue in obese individuals releases pro-inflammatory cytokines and free fatty acids that interfere with insulin signaling pathways and impair glucose uptake in peripheral tissues. Additionally, obesity reduces levels of adiponectin, a hormone that enhances insulin sensitivity, and contributes to mitochondrial dysfunction and oxidative stress, further worsening insulin resistance. Epidemiological studies consistently show that individuals with a higher body mass index (BMI) have a substantially increased risk of developing T2DM, and even modest weight loss can significantly improve insulin sensitivity and glycemic control. Therefore, while diabetes mellitus has multiple etiological factors, obesity plays a central role in its onset and progression, highlighting the need for targeted interventions aimed at weight management and lifestyle modification to prevent and manage this global health concern.

The Role of Obesity in Diabetes

The primary causes of diabetes include genetic predisposition, autoimmune destruction of pancreatic β-cells (Type 1 diabetes), and lifestyle factors such as obesity, poor diet, and physical inactivity (Type 2 diabetes). Among these, obesity is a key risk factor, particularly for Type 2 diabetes, as excess adipose tissue, especially visceral fat, leads to insulin resistance by releasing pro-inflammatory cytokines (e.g., TNF-α, IL-6) and free fatty acids, which impair insulin signaling. Obesity also contributes to lipotoxicity, pancreatic β-cell dysfunction, and chronic low-grade inflammation, further worsening glucose metabolism. The global rise in obesity, driven by sedentary lifestyles and high-calorie diets, has significantly increased the prevalence. Addressing obesity through weight management, lifestyle modifications, and metabolic interventions is crucial for diabetes prevention and treatment, with therapies like GLP-1 receptor agonists (e.g., Semaglutide) and bariatric surgery showing promising results in improving insulin sensitivity and glycemic control.

2.2 Hormonal Factors

2.2.1 Hormonal Changes (Gestational Diabetes)

Gestational diabetes is a type of diabetes that occurs during pregnancy and affects how the body processes glucose. It typically develops in the second or third trimester and is characterized by high blood sugar levels that are not usually present before pregnancy. The condition arises when the placenta produces hormones that interfere with insulin's ability to regulate blood sugar, leading to insulin resistance. While gestational diabetes often resolves after childbirth, it can increase the risk of developing Type 2 diabetes later in life for both the mother and child. Effective management involves monitoring blood sugar levels regularly, adhering to a balanced diet, engaging in regular physical activity, and, if necessary, using insulin or oral medications. Women with gestational diabetes should receive follow-up care to monitor their glucose levels postpartum and ensure the

condition has resolved. Proper management is crucial to minimize risks to both the mother and the baby, including complications such as excessive birth weight, preterm delivery, and preeclampsia. [17-22].

2.2.2 Polycystic Ovary Syndrome (PCOS)

Women with PCOS have an increased risk of insulin resistance and Type 2 diabetes due to hormonal imbalances affecting insulin action. Polycystic Ovary Syndrome (PCOS) is a hormonal disorder that affects women, and one of the significant reasons it increases the risk of developing diabetes, particularly Type 2 diabetes, is due to insulin resistance. Insulin is a hormone that helps the body process glucose from the bloodstream and use it for energy. Many women with PCOS have higher levels of insulin because their bodies do not respond properly to it, a condition known as insulin resistance. This forces the body to produce more insulin to try and maintain normal blood sugar levels.

Over time, elevated insulin levels can lead to a range of problems, including increased fat storage, weight gain, and difficulty managing blood sugar levels, which contribute to the development of Type 2 diabetes. Furthermore, the hormonal imbalances in PCOS, such as elevated androgens (male hormones), can exacerbate insulin resistance and metabolic issues, making it harder to regulate blood sugar.

The connection between PCOS and diabetes is also influenced by obesity, which is more common in women with PCOS. Obesity itself is a significant risk factor for insulin resistance and diabetes. Additionally, women with PCOS often have difficulty losing weight, which further complicates the regulation of blood sugar levels. [23].

3. Current Management Strategies

Current management strategies for diabetes mellitus (DM) encompass a comprehensive approach involving lifestyle modifications, pharmacological treatments, technological advancements, and patient education. Lifestyle modifications form the cornerstone of diabetes management, emphasizing a balanced diet, regular physical activity, and behavioral changes to maintain optimal weight and improve insulin sensitivity. Dietary recommendations focus on controlling carbohydrate intake, increasing fiber, and reducing saturated fats, while physical activity aids in lowering blood glucose levels and enhancing cardiovascular health.

Pharmacological treatments vary depending on the type of diabetes. In Type 1 diabetes (T1D), insulin therapy is essential and tailored to mimic natural insulin secretion patterns. This includes basal (long-acting) insulin to manage fasting blood glucose and bolus (short-acting) insulin to control postprandial spikes. For Type 2 diabetes (T2D), oral hypoglycaemic agents such as metformin, sulfonylureas, and DPP-4 inhibitors are commonly used to improve insulin sensitivity and stimulate insulin secretion. One of the most promising areas is the development of novel drug classes, such as GLP-1 receptor agonists, SGLT2 inhibitors, and DPP-4 inhibitors, which not only enhance glycaemic control but also offer cardiovascular and renal benefits. Additionally, newer injectable medications like GLP-1 receptor agonists and SGLT2 inhibitors provide advantages in glucose control and weight management.

Technological innovations have significantly enhanced diabetes management. Continuous glucose monitoring (CGM) systems provide real-time data on blood glucose levels, assisting patients and healthcare providers in making informed decisions about treatment adjustments. Insulin pumps, particularly those integrated with CGM systems within closed-loop systems (artificial pancreas), automate insulin delivery, alleviating the burden of constant blood glucose monitoring and insulin administration.

Patient education and support are critical components of effective diabetes management. Structured diabetes education programs empower patients with knowledge and skills to manage their condition, including understanding the importance of blood glucose monitoring, recognizing symptoms of hypo- and hyperglycaemia, and adhering to treatment plans. Support from healthcare providers, diabetes educators, and support groups can enhance self-management, improve adherence to treatment, and address psychological aspects of living with diabetes.

3.1 Lifestyle Modifications

Lifestyle modifications are a cornerstone of diabetes management, helping to control blood sugar levels, prevent complications, and improve overall health. A balanced diet is essential, focusing on whole grains, lean proteins, healthy fats, and plenty of fruits and vegetables, while monitoring carbohydrate intake and practicing portion control to avoid blood sugar spikes. Regular physical activity, such as walking, cycling, or swimming, enhances insulin sensitivity and supports weight management, both crucial for controlling Type 2 diabetes. Weight loss for those who are overweight can significantly improve blood sugar control, reducing the need for medications. Additionally, managing stress through techniques like meditation, yoga, and mindfulness is important, as chronic stress can raise blood sugar levels. Establishing good sleep habits is also important, as poor sleep can affect insulin sensitivity. Finally, regular blood sugar monitoring and medical checkups are vital for tracking progress and detecting potential complications early. These lifestyle changes, when consistently followed, can greatly improve the quality of life for people living with diabetes [28, 29].

3.2 Pharmacological Interventions

Pharmacological treatments vary based on diabetes type and individual patient needs. For T1DM, insulin therapy is essential. T2DM management includes oral hypoglycemic agents, such as metformin, sulfonylureas, and newer agents like DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors. Combination therapy is often necessary to achieve glycemic targets [30].

3.3 Monitoring and Glycaemic Control

Regular monitoring of blood glucose levels is critical for effective diabetes management. Self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM) systems provide real-time data, allowing for timely adjustments in therapy. Glycated hemoglobin (HbA1c) is a key marker for long-term glycemic control.

Overall, the integration of lifestyle modifications, pharmacological treatments, technological advancements, and robust patient education and support systems forms a multifaceted approach to effectively manage diabetes, minimize complications, and improve the quality of life for individuals with diabetes [31].

4. Emerging Therapeutic Approaches

4.1 Novel Pharmacotherapies

New pharmacotherapies are being developed to improve diabetes management. These include drugs targeting insulin resistance, beta-cell preservation, and glucose regulation. Dual agonists and novel insulin formulations are showing promise in clinical trials.

Emerging therapeutic approaches and novel pharmacotherapies for diabetes aim to improve blood sugar control, reduce complications, and offer more personalized treatments for patients. These new developments are transforming diabetes care, particularly for those with Type 2 diabetes and difficult-to-control cases. Here are some of the most promising innovations:

4.1.1 SGLT2 Inhibitors (Sodium-Glucose Cotransporter-2 Inhibitors)

This class of drugs works by preventing the kidneys from reabsorbing glucose, causing excess sugar to be excreted in the urine. SGLT2 inhibitors, such as empagliflozin and dapagliflozin, not only help lower blood sugar but also offer cardiovascular and renal protective effects, making them beneficial for patients at risk of heart and kidney disease.

4.1.2 GLP-1 Receptor Agonists (Glucagon-like Peptide-1 Receptor Agonists)

Drugs like liraglutide and semaglutide mimic the action of the GLP-1 hormone, which stimulates insulin production, suppresses glucagon release, and slows gastric emptying. These effects help control blood sugar, reduce appetite, and promote weight loss. GLP-1 receptor agonists also provide cardiovascular benefits, reducing the risk of heart disease in people with diabetes.

4.1.3 Dual GIP/GLP-1 Receptor Agonists

This is a newer class of medications that targets both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors. The dual action improves glucose control, enhances insulin sensitivity, and promotes weight loss more effectively than traditional GLP-1 agonists. One example is tirzepatide, which is showing promise in clinical trials for its superior glycaemic control and weight loss benefits.

4.1.4 DPP-4 Inhibitors (Dipeptidyl Peptidase-4 Inhibitors)

DPP-4 inhibitors, such as sitagliptin and saxagliptin, work by preventing the breakdown of GLP-1, allowing the body to produce more insulin in response to high blood sugar. These medications help improve glucose levels with a low risk of hypoglycaemia and are often used in combination with other therapies.

4.1.5 Stem Cell Therapy and Beta-Cell Regeneration

Research into stem cell therapy focuses on regenerating the insulin-producing beta cells of the pancreas. In Type 1 diabetes, where the immune system destroys beta cells, the potential to regenerate or replace these cells could revolutionize treatment. Early trials involving stem cell-derived islet cells show promise in restoring insulin production and reducing the need for external insulin.

4.1.6 Artificial Pancreas Systems (Closed-Loop Insulin Delivery)

The artificial pancreas is an advanced form of insulin delivery that combines a continuous glucose monitor (CGM) with an insulin pump to automate insulin administration. These closed-loop systems adjust insulin delivery in real-time based on blood sugar levels, reducing the need for manual adjustments and improving glucose control for patients with Type 1 diabetes.

4.1.7 Gene Therapy

Gene therapy for diabetes is an experimental approach that aims to correct the genetic defects that cause or contribute to diabetes. Scientists are exploring ways to modify genes to improve insulin production or sensitivity, with early animal studies showing potential. Though still in the early stages, gene therapy could provide long-term solutions for managing or even curing diabetes in the future.

4.1.8 Smart Insulin and Glucose-Responsive Insulin

Smart insulin is being developed to respond to blood sugar levels, releasing insulin only when glucose levels are high. This would reduce the risk of hypoglycemia and provide a more natural insulin response. Glucose-responsive insulin formulations are designed to mimic the body's own insulin production, offering more precise control over blood sugar levels.

4.1.9 Fexuprazan: A Novel GLP-1/GCGR Dual Agonist

This experimental therapy targets both GLP-1 receptors and glucagon receptors (GCGR). The dual action of fexuprazan not only improves glucose control but also increases energy expenditure, potentially helping with weight loss and better overall metabolic outcomes.

4.1.10 Nanotechnology in Diabetes Treatment

Nanotechnology-based treatments are being explored to create more efficient drug delivery systems. Nanoparticles can deliver insulin or other medications directly to specific tissues, improving drug efficacy, reducing side effects, and allowing for longer intervals between doses.

These emerging therapeutic approaches and novel pharmacotherapies are expanding the options for diabetes management, offering more effective, convenient, and personalized care for people living with diabetes. They hold the potential to not only improve blood sugar control but also address the underlying metabolic issues and reduce the risk of complications [32, 33].

4.2 Technological Advancements

Advances in technology are revolutionizing diabetes care. Insulin pumps and closed-loop systems (artificial pancreas) offer more precise insulin delivery. Emerging therapeutic approaches for diabetes are increasingly driven by technological advancements that are improving blood sugar control and simplifying disease management. Continuous glucose monitoring (CGM) systems provide real-time data on glucose levels, allowing patients to track trends and receive alerts for highs and lows without constant finger-prick tests. Artificial pancreas systems, which combine CGMs with insulin pumps, offer closed-loop insulin delivery, automating insulin administration based on glucose readings. This reduces the burden on patients, particularly those with Type 1 diabetes. Smart insulin pens and advanced insulin pumps with predictive algorithms enhance dosing accuracy, helping to prevent blood sugar fluctuations. Telemedicine and mobile health apps enable remote consultations and allow patients to share glucose

data with healthcare providers, ensuring more personalized and convenient care. Emerging technologies, such as non-invasive glucose monitoring through optical sensors or patches, and smart insulin that responds to glucose levels, aim to make diabetes management even less invasive and more responsive. Artificial intelligence (AI) and machine learning are also being used to predict glucose trends and optimize treatment plans, further enhancing personalized care. Together, these advancements are transforming diabetes management, making it more automated, precise, and patient-friendly [34, 35].

4.3 Potential Curative Strategies

Potential curative strategies that aim to address the root causes of the disease, particularly in Type 1 diabetes and some cases of Type 2 diabetes. One of the most promising areas is stem cell therapy, which seeks to regenerate insulin-producing beta cells in the pancreas. By replacing the damaged or destroyed beta cells with functional ones, stem cell treatments could restore the body's ability to produce insulin naturally. Early trials using stem cell-derived islet cells have shown potential in reducing or eliminating the need for external insulin. Another potential curative approach is gene therapy, which aims to correct the genetic defects that contribute to diabetes. By modifying or repairing specific genes that impact insulin production or glucose metabolism, gene therapy could offer a long-term solution for managing or even curing the disease. Additionally, immune therapies are being explored to prevent the autoimmune attack on beta cells in Type 1 diabetes, with the hope of halting the disease before significant damage occurs. Pancreas transplants and islet cell transplants are also curative strategies already in use for some patients, offering the possibility of insulin independence, though these are often limited by the need for immunosuppressive drugs. Together, these curative strategies hold the potential to not only manage but potentially reverse diabetes, offering hope for a future where insulin dependence is no longer necessary [36, 37].

5. Future Directions and Research

Future directions and research for diabetes are set to revolutionize the management and potential cure of the disease. Advanced glucose monitoring technologies, including non-invasive sensors and more integrated continuous glucose monitors (CGMs), aim to provide more accurate and user-friendly data. Artificial intelligence and machine learning are being harnessed to analyse patient data, predict glucose trends, and personalize treatment plans with greater precision. Gene therapy and CRISPR gene-editing technologies hold promise for correcting genetic defects and enhancing insulin production. In parallel, stem cell research seeks to regenerate or replace damaged insulin-producing beta cells, potentially restoring natural insulin production. Immunotherapy is exploring ways to halt the autoimmune destruction of beta cells in Type 1 diabetes. Personalized medicine approaches are focusing on tailoring treatments based on individual genetic and metabolic profiles, while novel pharmacotherapies and advanced insulin delivery systems aim to improve treatment efficacy and convenience. Additionally, research into metabolic surgery and the development of new lifestyle and behavioural interventions continues to refine strategies for managing diabetes. These innovative directions and research efforts are poised to enhance diabetes care, offering the hope of more effective treatments and possibly even a cure.

Globally, prevention strategies are critical, including lifestyle interventions that promote healthy eating, physical activity, and weight management, alongside early detection programs to identify at-risk individuals. Policy and advocacy efforts are essential to support these initiatives, advocating for public health policies that prioritize diabetes prevention, education, and management. Strengthening international collaboration will facilitate the sharing of knowledge, resources, and best practices. Lastly, integrating healthcare approaches that involve interdisciplinary teams and patient-centered care models will ensure comprehensive and effective diabetes management, addressing the diverse needs of individuals living with diabetes.

6. Conclusion

Diabetes mellitus remains a major global health challenge, but significant advancements in understanding its pathophysiology and management are being made. Current treatment strategies focus on lifestyle modifications, pharmacotherapy, and monitoring to achieve glycaemic control and prevent complications. Emerging therapeutic approaches, including novel drugs, technological innovations, and potential curative strategies, offer hope for improved outcomes and quality of life for individuals with diabetes. Ongoing research and development are essential to address the evolving needs of diabetes care. Effective strategies to combat obesity will play a pivotal role in reducing the global burden of diabetes and improving the quality of life for individuals at risk.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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