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DIABETES MELLITUS: A COMPREHENSIVE REVIEW OF PATHOPHYSIOLOGY, EPIDEMIOLOGY, CLINICAL MANAGEMENT, AND FUTURE DIRECTIONS

Pharmacy Practice

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ABSTRACT

Diabetes, also called type 2 diabetes, is a big medical issue around the world, affects thousands of millions of people. The number of people who get it is rising each year, especially in low- and middle-income nations. This review examines how diabetes has grown and spread worldwide, focusing on the main causes of Diabetes with type 1 with type 2 (T1D) and T2D): autoimmune destruction of pancreatic beta cells and insulin resistance, respectively. This study examines how management approaches, such as lifestyle changes, medication, and new technologies, affect health outcomes. The text also discusses how more people are being diagnosed with diabetes, how to identify it, current treatments, personalised treatment plans, and how public health policy can help prevent and manage the disease. The goal is to make diabetes easier to understand and stress the need for more research and better treatment.

KEYWORDS

diabetes mellitus, pathophysiology, epidemiology, clinical management, future directions, insulin resistance, β-cell dysfunction

INTRODUCTION

Diabetes is a long-term health issue where blood sugar gets too high. As per 2021 data, approximately 537 million adults are living with diabetes globally, and this figure is projected to increase to 783 million by 2045 [1], which shows a significant rise in prevalence. Figuring out why it happens, what makes it more likely, and how to deal with it. for diabetes is important as the number of affected individuals continues to grow worldwide.

Type 1 diabetes (T1D) and type 2 diabetes (T2D) are the most prevalent forms of diabetes, with T1D being an autoimmune disorder that leads to the destruction of pancreatic beta cells and results in complete insulin deficiency [2]. T2D accounts for nearly 90–95% of all diabetes cases and is mainly associated with insulin resistance and inadequate insulin secretion, which is often related to obesity and lifestyle factors [3]. Other types include gestational diabetes mellitus (GDM), diabetes due to specific genetic mutations, and cases arising from pancreatic diseases or the use of certain medications [4].

This review discusses the development and prevalence of diabetes, current approaches to management, and future directions for research. The main goal is to provide doctors and nurses, researchers, and policymakers with a comprehensive summary of recent findings and to highlight the most important areas that require further research and action.

PATHOPHYSIOLOGY

TYPE 1 DIABETES (T1D)

Type 1 diabetes is the thing that makes it hard for people to control the amount of sugar in their blood. The immune system's targeted destruction of pancreatic β-cells leads to total insulin deficiency [2]. The pathogenesis entails a multifaceted interaction between genetic predisposition and environmental factors. The human leukocyte antigen (HLA) region, particularly HLA-DR3 and HLA-DR4, is a significant genetic locus associated with an elevated risk [5]. Environmental factors, including viral infections (e.g., enteroviruses), dietary influences, and early-life exposures, are believed to initiate or accelerate β-cell autoimmunity [6].

The autoimmune process is marked by the presence of autoantibodies targeting β-cell antigens, such as insulin, the enzyme glutamic acid decarboxylase (GAD65), islet antigen 2 (IA-2), and the zinc transporter 8 (ZnT8) [7]. These antibodies can be detected years before the disease starts, making it easier to identify people at risk. The gradual destruction of β-cells causes insulin secretion to be less effective, which leads to high blood sugar levels and the typical signs of diabetes, such as experiencing excessive thirst, frequent urination, and weight loss [2].

TYPE 2 DIABETES (T2D)

Diabetes type 2 is a diverse condition influenced by the interaction of environmental, genetic, and behavioural factors. The main problems are insulin resistance in peripheral tissues (especially muscle, liver, and adipose tissue) and β-cell dysfunction that worsens over time [8]. Insulin resistance often precedes hyperglycemia. For many years, β-cells initially compensated by secreting more insulin. But over time, β-cell failure occurs, leading to diabetes [9].

Insulin resistance is caused by several pathophysiological mechanisms, including ectopic lipid accumulation, swelling, mitochondrial dysfunction, and endoplasmic reticulum stress [10]. Inflammation of adipose tissue, characterised by macrophage infiltration and cytokine release, is a major cause of systemic insulin resistance [11]. When the liver becomes insulin-resistant, it produces more glucose, which elevates fasting blood sugar levels [12]. Figure 1:

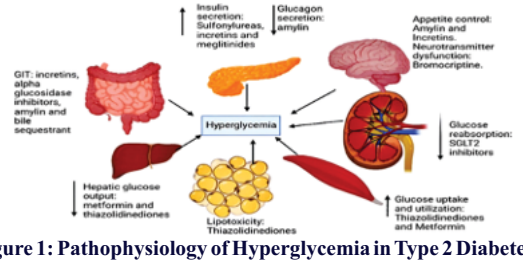

Figure 1: Pathophysiology of Hyperglycemia in Type 2 Diabetes

In T2D, β-cells don't function properly, meaning they don't release insulin properly, die more often, and lose their specialised functions [13]. Genetic factors affect the function and mass of β-cells. More than

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400 genetic loci are linked to T2D risk, and many of these loci are associated with β-cell development and function [14]. The progressive nature of T2D reflects β-cell failure to adapt to increasing insulin resistance, which is frequently exacerbated by glucotoxicity, lipotoxicity, and amyloid deposition [15]. (Fig 1)

EPIDEMIOLOGY

Diabetes mellitus (DM) has evolved into a significant health issue globally. With the prevalence increasing rapidly in recent years. The International Diabetes Federation (IDF) says that in 2021, 10.5% of adults aged 20-79 had diabetes, totaling 537 million people worldwide. The Western Pacific region reported the highest number of cases, with more than 206 million people, followed by South-East Asia and Europe. These statistics indicate that diabetes is having a significant and expanding impact across various regions. [16]

In the coming years, the number of people living with diabetes is expected to increase significantly, primarily caused by factors such as growing populations, ageing, urbanisation, rising obesity rates, and decreased physical activity. According to IDF estimates, the global diabetes population will reach 783 million by 2045, a 46% increase from current figures. The largest rise is anticipated in low- and middle-income countries, primarily because of changing health patterns and increased life expectancy.[17]

TYPE 1 DIABETES EPIDEMIOLOGY

Type 1 diabetes constitutes about 5–10% of the cases of diabetes and ranks among the most common long-term illnesses in kids and young adults [18]. The number of people with T1D worldwide varies widely. Finland has the highest rates (over 60 per 100,000 per year), while some Asian and African countries have the lowest rates (less than 1 per 100,000 per year) [19]. Incidence rates have been rising worldwide, especially among younger people. In many places, they increase by about 3–4% each year [20].

Genetic variables play a crucial role in shaping the development of Type 1 Diabetes (T1D). with a sibling risk ratio of about 15 and a concordance rate of 30–50% in monozygotic twins [21]. Environmental factors, such as viral infections, early diet, and gut microbiome composition, are believed to play a role in disease onset, although the exact mechanisms remain poorly elucidated [22].

TYPE 2 DIABETES EPIDEMIOLOGY

Type 2 diabetes is the most common form of diabetes worldwide and is closely linked to risk factors that can be changed, such as being overweight, lack of physical activity, and unhealthy eating habits.[23] T2D is especially common among older adults, with more than 20% of people aged 65 years and above affected in many countries. However, the incidence of T2D is also rising among younger age groups, including adolescents and young adults, mainly because of the increasing rates of obesity.[24]

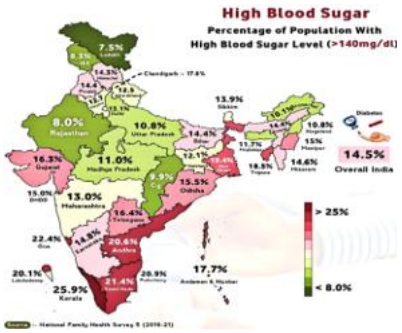
There are significant differences in T2D rates across ethnic and racial groups. For example, African, Hispanic, Asian, and Indigenous populations have higher rates than European populations [25]. These disparities are indicative of variations in genetic susceptibility, socioeconomic determinants, healthcare accessibility, and lifestyle factors [26].

MORTALITY AND BURDEN OF COMPLICATIONS

Diabetes is a major cause of death around the world, with an estimated 6.7 million people dying from it in 2021 [1]. People with diabetes are two to three times more likely to get cardiovascular disease (CVD) than people who don't have diabetes. CVD is responsible for about half of all deaths in this group [27].

Microvascular issues are a big reason people get sick. Diabetic retinopathy is the primary cause of blindness worldwide. Diabetes costs health systems a lot of money. In 2021, about $966 billion was spent on diabetes globally, a 316% increase from 15 years earlier. The majority of these costs are allocated to medical care, hospitalisation, medications, management of complications, and loss of productivity due to disability. ney goes to medical care, hospital stays, medications, treating complications, and lost productivity from disability.[28] (Fig 2)

CLINICAL MANAGEMENT



DIAGNOSIS AND CLASSIFICATION

Several methods exist for diabetes diagnosis. These assessments encompass the fasting plasma glucose test, the 2-hour plasma glucose test after a 75-g oral glucose tolerance test, haemoglobin A1c testing, and random plasma glucose testing when classic symptoms are present [29].

The World Health Organization (WHO) and the American Diabetes Association (ADA) say that the following levels of glucose in the blood are diagnostic: FPG ≥ 7.0 mmol/L (126 mg/dL), 2-h PG ≥ 11.1 mmol/L (200 mg/dL), HbA1c ≥ 6.5% (48 mmol/mol), or random glucose ≥ 11.1 mmol/L (200 mg/dL) with symptoms [30].

For proper treatment, it is important to identify the specific type of diabetes. Type 1 diabetes (T1D) usually has a rapid onset, is associated with ketosis, a lean body type, and the presence of autoantibodies. Type 2 diabetes (T2D) develops more gradually and is commonly linked to obesity and metabolic syndrome [2]. Some individuals may show features of both types, which requires a thorough clinical evaluation [31].

LIFESTYLE INTERVENTIONS

Lifestyle modification is the most important aspect of diabetes management, especially for the prevention and treatment of type 2 diabetes. Dietary interventions focus on achieving and maintaining a healthy weight, improving glycaemic control, and reducing the risk of cardiovascular disease [32]. Various diets, including the Mediterranean diet, DASH (Dietary Approaches to Stop Hypertension), and plant-based diets, have shown benefits for people with diabetes [33]. Monitoring carbohydrate intake and using the glycaemic index or glycaemic load are also effective strategies for maintaining stable blood sugar levels [34].

Individuals with diabetes should engage in physical activity for at least 150 minutes per weekof moderate-intensity aerobic exercise per week, along with resistance. Engaging in physical training two to three times per week can help improve insulin action [35]. Routine exercise supports blood sugar regulation, heart health, and weight control [36]. Behavioral strategies, such as education, goal setting, and self-checks, also play a key role in sustaining long-term lifestyle changes [37].

PHARMACOTHERAPY

TYPE 1 DIABETES

Insulin therapy is necessary for individuals with T1D to survive, typically commencing with multiple injections. People with T1D need insulin therapy to stay alive, which usually starts with multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) through an insulin pump [38]. Intensive insulin therapy uses basal (long-acting insulin analogues) and bolus (rapid-acting insulin analogues) insulin to mimic the body's normal insulin release [39]. Basal-bolus therapy with insulin glargine or detemir and rapid-acting insulin, such as lispro or glulisine, is a common treatment plan [40]. Better glucose control and reduced insulin requirements have been observed [41]. At the moment, there are no oral medications or injectable drugs other than insulin that are approved to treat Type 1 Diabetes (T1D) alone. Studies on methods to modulate the immune system and replace β-cells are ongoing [42].

TYPE 2 DIABETES

The pharmacological treatment of T2D has significantly advanced, offering a wide array of glucose-lowering agents. For most patients, metformin is still the first-line oral agent. It mostly works by lowering the amount of glucose the liver produces and by making insulin more effective [43].

Sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists are all second-line treatments [44]. Choosing an agent must be based on its effectiveness, the risk of hypoglycemia, its effect on weight, cardiovascular outcomes, kidney function, cost, and the patient's preferences [45].

SGLT2 inhibitors and GLP-1 receptor agonists are preferred treatments for people with atherosclerotic cardiovascular disease (CVD) or chronic kidney disease (CKD) because they benefit both the heart and the kidneys [46]. SGLT2 inhibitors lower the risk of heart problems and hospitalisation's for heart failure, and they also slow the progression of diabetic kidney disease [47]. GLP-1 receptor agonists help people lose weight and lower the risk of major adverse cardiovascular events (MACE) [48].

MONITORING AND GLYCEMIC TARGETS

People with diabetes may monitor their blood sugar levels through self-monitoring of blood glucose (SMBG), continuous glucose monitoring (CGM), and checking their long-term glycaemic control with HbA1c [49]. CGM systems provide real-time glucose data, patterns, and alerts that help you better control your blood sugar and lower your risk of hypoglycemia, especially if you have T1D [50].

The normal goal for most adults who aren't pregnant is an HbA1c level below 7% (53 mmol/mol). Some people may need stricter targets (below 6.5% or 48 mmol/mol), while others with many other health problems should aim for less strict targets (below 8% or 64 mmol/mol) [4]. It is very important to lower the risk of heart disease, which includes controlling blood pressure (for most patients, the goal is less than 130/80 mmHg), managing lipids (for patients at least 40 years old, statin therapy is recommended), and taking antiplatelet therapy (also known as aspirin for secondary prevention) [51]. For people with diabetes who have high blood pressure, renin-angiotensin-aldosterone system (RAAS) inhibitors are better [52].

FUTURE DIRECTIONS

EMERGING THERAPIES

Research into new ways to treat diabetes continues. In type 1 diabetes (T1D), researchers are investigating immunomodulatory agents such as anti-CD3 (teplizumab) and anti-CD20 (rituximab) antibodies to preserve β-cell function. Teplizumab was recently approved by the FDA to delay the onset of clinical Type 1Diabetes in people who are at risk [53]. Islet cell transplantation and stem cell-derived β-cells are two types of β-cell replacement therapies that could help people live without insulin [54].

In individuals with type 2 diabetes (T2D), dual and triple incretin agonists, including the tripeptide (a GIP/GLP-1 receptor agonist), have shown enhanced glycaemic control and weight reduction compared with single incretin therapies [55]. New drugs targeting other pathways, such as glucagon receptor antagonists, free fatty acid receptor agonists, and mitochondrial uncouplers, are currently under development [56].

PRECISION MEDICINE

Precision medicine seeks to customise diabetes prevention and treatment based on each person's unique genetic, phenotypic, and environmental traits. Genetic risk scores can pinpoint individuals at elevated risk for T2D, facilitating targeted preventive measures [57]. Grouping patients with diabetes by genetic and clinical information could help personalize treatment [58]. Pharmacogenetics can predict responses to drugs such as sulfonylureas and GLP-1 receptor agonists, but it's not widely used in clinical practice yet [59].

TECHNOLOGY AND DIGITAL HEALTH

New technologies for diabetes, such as CGM, insulin pumps, and closed-loop systems (an artificial pancreas), are changing how diabetes is managed. Closed-loop systems that continually adjust insulin dosing based on continuous glucose monitor readings have shown better glycaemic control and fewer hypoglycemic episodes in both type 1 and type 2 diabetes [60].

Digital health methods such as mobile apps, telemedicine, and coaching sites help people manage their own health and access care, especially those who don't have good access [61]. Researchers are working on algorithms using machine learning and AI that can find patients who are at risk of complications, figure out the best insulin dose, and predict glycaemic excursions [62].

5.4 PREVENTION STRATEGIES

The Program for Diabetes Prevention and the Finnish Insulin Prevention Research Project are two examples of randomised controlled trials that have shown that lifestyle changes can help prevent T2D. These 5–7% through diet and exercise can lower the risk of diabetes by about 58% in people who are already at risk [63]. To turn these results into strategies for the whole population, we need to examine food systems, physical activity settings, and the socioeconomic factors that affect health [64].

Fiscal measures such as taxes on sugary drinks, front-of-pack labelling, restrictions on marketing unhealthy foods to kids, and urban planning that encourages active lifestyles are examples of population-based prevention strategies [65]. In the United States, the National Diabetes Prevention Program (NDPP) and other community-based programs have been established to help at-risk individuals follow structured lifestyle plans [66].

SPECIAL POPULATIONS

PEDIATRIC DIABETES

Type 1 diabetes (T1D) is the most common type of diabetes in children and teens, but type 2 diabetes (T2D) is becoming more common, especially in the context of childhood obesity [67]. Managing diabetes in children requires care that is appropriate for their age, such as insulin therapy, nutritional counselling, and psychosocial support [68]. The shift from paediatric to adult diabetes care is a critical period associated with deteriorating glycaemic control and an increased risk of complications [69].

GESTATIONAL DIABETES

Gestational diabetes mellitus (GDM) affects about 14% of pregnancies worldwide, and this number is going up because more women are becoming obese [70]. Screening and diagnosis usually occur between 24 and 28 weeks of pregnancy with a 75-g OGTT [4]. Management encompasses medical nutrition therapy, exercise, and insulin therapy, with oral drugs (metformin, glyburide) deemed acceptable in certain contexts [71]. After giving birth, follow-up is important to assess the mother's glucose metabolism and provide guidance on planning for future pregnancies and avoiding diabetes [72].

DIABETES IN OLDER ADULTS

More and more older adults with diabetes are having trouble managing their condition because they are more likely to have low blood sugar, take multiple medications, experience cognitive decline, and have trouble doing everyday tasks [73]. Glycaemic goals should be different for each person. For people with a short life expectancy or many other health problems, the goals should be less strict (e.g., HbA1c < 8.0% or 64 mmol/mol) [4]. Even though blood pressure goals may not be as strict for frail people, it is still important to control cardiovascular risk factors, such as high blood pressure and dyslipidemia [74].

CONCLUSION

Diabetes mellitus continues to be a significant global health issue, impacting hundreds of millions of people and placing a considerable burden on individuals, families, and healthcare systems. This review has discussed the main causes of diabetes, such as autoimmune disorders and beta-cell destruction in type 1 diabetes, and the relationship between insulin resistance and beta-cell dysfunction in type 2 diabetes. The increasing prevalence of diabetes is closely linked to rising obesity rates and reduced physical activity, with the most rapid growth expected in low- and middle-income countries. Advances in medicines, technologies, and healthcare delivery have improved diabetes management. Lifestyle modification remains the most important part of treatment, while newer drugs like SGLT2 inhibitors and GLP-1 receptor agonists provide additional benefits for blood sugar control and protection of the heart and kidneys. Technologies including closed-loop systems, continuous glucose monitoring, and digital health tools are also transforming diabetes care. However, ensuring equal access to care for all remains a challenge. Addressing the diabetes epidemic requires strategies focused on prevention, early detection, and improved access to quality healthcare. Reducing the global impact of diabetes will need coordinated efforts from healthcare professionals, researchers, policymakers, and communities.

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CONFLICT OF INTEREST: None

Abbreviations

DM – Diabetes Mellitus
T1DM – Type 1 Diabetes Mellitus
T2DM – Type 2 Diabetes Mellitus
GDM - Gestational Diabetes Mellitus
NCDs - Non-Communicable Diseases
SMBG – Self-Monitoring of Blood Glucose
DASH - Dietary Approaches to Stop Hypertension
CGM - Continuous Glucose Monitoring

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