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Diabetes Mellitus: A Complete Review

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ABSTRACT:

Elevated blood glucose levels are a hallmark of diabetes mellitus (DM), a chronic metabolic condition caused by insufficient insulin synthesis (Type 1 DM), insulin resistance (Type 2 DM), or other specific reasons. It is a major global health concern that affects millions of people globally and has a considerable impact on morbidity and mortality. With a focus on the changing landscape of therapeutic approaches, this review offers an updated overview of the etiology, diagnosis, therapy, and consequences of diabetes mellitus. The intricate pathophysiology of diabetes mellitus encompasses genetic, environmental, and immune variables. An absolute lack of insulin results from the autoimmune destruction of pancreatic beta cells in Type 1 diabetes, whereas insulin resistance and a relative decrease in insulin output are the main characteristics of Type 2 diabetes. A sedentary lifestyle, genetic susceptibility, and obesity are major factors in the rising incidence of Type 2 diabetes. Furthermore, the varied nature of diabetes is highlighted by certain forms of the disease, such as monogenic diabetes, and gestational diabetes. It is essential to treat diabetes properly and diagnose patients early to avoid complications. Hemoglobin A1c readings, oral glucose tolerance tests, and fasting blood glucose levels are commonly used to make the diagnosis. Type 2 DM is treated with a mix of lifestyle changes, oral hypoglycemic medications, and, in certain situations, insulin therapy. Type 1 DM needs insulin replacement therapy.

Keywords: Diabetes mellitus, Type 1 diabetes, Type 2 diabetes, insulin resistance, hyperglycemia, glycemic control, complications, cardiovascular disease, SGLT-2 inhibitors, GLP-1 receptor agonists, continuous glucose monitoring, insulin therapy, metabolic disorder, pathophysiology, pharmacological treatments, public health.

INTRODUCTION:

A major public health concern, the rising prevalence of diabetes mellitus places unsustainable demands on people, their careers, healthcare institutions, and society. According to the most recent projections, 425 million individuals worldwide had diabetes in 2017, and by 2045, that number is predicted to climb to 629 million. This is fueled by the rising incidence of obesity and unhealthy behaviours including poor diets and inactivity, which are in turn encouraged by broader socioeconomic variables such as global shifts in nutrition (the so-called "nutrition transition"). Type 2 diabetes makes up the majority (>85%) of all cases of diabetes mellitus, according to the aetiological categorization of diabetes, which divides diabetes mellitus into two main types: type 1 and type 2. Both prevalent kinds of diabetes can result in multisystem consequences, including microvascular endpoints like retinopathy, nephropathy, and neuropathy, as well as macrovascular endpoints like ischemic heart disease, stroke, and peripheral vascular disease. Type 1 diabetes still has its etiology up for debate. With a better understanding of the role that modifiable factors play in the development of type 2 diabetes, prevention has become a viable public health objective. Diabetes is a metabolic disorder with several etiologies that also alter the metabolism of carbohydrates, lipids, and proteins as a result of issues with insulin production, action, or both. Chronic hyperglycaemia (elevated blood glucose levels) is a characteristic of diabetes. Hyperglycaemia causes the development of diabetic complications, which result from long-term harm, malfunction, and failure of many organs and bodily functions that affect health and quality of life. Diabetes has a significant negative impact on several body systems and organs, including the cardiovascular and circulatory system (cardiovascular disease), kidneys (nephropathy), brain and cerebral circulatory system (cerebrovascular disease, stroke, cognitive dysfunction), lower limbs (peripheral vascular disease, diabetic foot), immune system (increased risk of infections), and eyes (retinopathy). Early signs may include thirst, excessive urination, blurred eyesight, and weight loss. Following a random venous blood glucose test, a fasting blood glucose test, a two-hour plasma glucose tolerance test after 75 g of oral glucose, or a non-fasting measurement of glycated haemoglobin (HbA1c), diabetes can be diagnosed. On people and their families, health systems, and national economies, diabetes and its consequences have a huge financial impact. Worldwide diabetes epidemics and related consequences carry enormous financial expenses that must be borne by patients and their families. Diabetes is one such comorbidity that affects more than 430 million people worldwide as of 2019 [1] and has the potential

to modify the natural history of COVID-19 unfavourably. Conversely, COVID-19 itself has been postulated to cause diabetes and to worsen glycaemic control in pre-existing diabetes.

1. Diabetes

Diabetes is a chronic disease. It is a metabolic disease caused by the dysfunction of beta cells and insulin resistance which increase blood glucose levels that show a deficiency of insulin in the body. Diabetes is classified into many types such as type 1 diabetes(T1D), type 2 diabetes(T2D), monogenic diabetes, gestational diabetes, and latent autoimmune diabetes but type 1 diabetes(T1D) and type 2(T2D) diabetes are the major types of diabetes. [1] Type 1 diabetes (T1D) is an autoimmune form of diabetes that shows early onset of action and type 1 diabetes(T2D) cannot be cured but it can be controlled if the treatment starts early. Type 2 diabetes (T2D) is a non-autoimmune form of diabetes that shows late onset of action and type 2 diabetes(T2D) also cannot be cured but some people reverse it to type 1 diabetes(T1D) by changing their diet and losing their weight. [2]

2. Classification and Types of Diabetes

Diabetes is a complex and heterogeneous disease that can be classified into different types based on etiology, clinical characteristics, and treatment approaches. This section discusses the following subheadings: Type 1 Diabetes, Type 2 Diabetes, Gestational Diabetes, and Other Specific Types.

2.1 Type 1 Diabetes and Type 2 Diabetes

Diabetes is of two types T1D and T2D. Insulin deficiency, which results in type 1 diabetes, is brought on by the autoimmune death of the Langerhans cells in the pancreatic islets (historically known as insulin-dependent diabetes mellitus). Lack of insulin makes it difficult to manage blood glucose levels, which causes hyperglycemia. It is thought that a genetic predisposition and an environmental trigger combine to cause type 1 diabetes (most probably, infection with an enterovirus). The majority of cases of type 1 diabetes, which make up between 5 and 10% of all occurrences of diabetes, tend to occur in childhood, adolescents, or young adults. Around 90% of diabetes cases are type 2, which is brought on by decreased insulin secretion and increased insulin resistance. Other names for type 2 diabetes include non-insulin-dependent diabetes mellitus (i.e., less insulin is produced, plus body cells are increasingly resistant to the effects of insulin, leading to hyperglycemia). The possibility of developing type 2 diabetes increases with age, with younger individuals and children now having a higher risk of developing it, and the majority of cases being discovered after the age of 40. Typically, lifestyle issues including being overweight or obese and not exercising are linked to it. Diabetes prevalence is rising. According to the International Diabetes Federation, there are 425 million diabetics worldwide (8.8% of individuals aged 20 to 79), and by 2045, there are expected to be 629 million. 5 A further million people in the UK have type 2 diabetes that has not yet been diagnosed, bringing the total number of persons with diabetes in the country to 3.7 million. The proportion of individuals in the UK with elevated HbA1c (but which has not yet reached the threshold for diagnosis of diabetes) is also increasing; 35.3% of adults in 2011 had HbA1c values in the range of 39– 46 mmol/mol (5.7– 6.4%) compared with 11.6% in 2003, indicating that large changes can occur at the population level within a relatively short period of time, raising concerns about the potential for future increases in diabetes prevalence.[3] Type 1 Diabetes is an autoimmune disease characterized by the destruction of insulin-producing beta cells in the pancreas, leading to absolute insulin deficiency. Usually, it starts to manifest in early adulthood or youth. To control their blood glucose levels, people with type 1 diabetes need to take insulin for the rest of their lives.[4] Type 2 Diabetes is the most common form of diabetes, accounting for the majority of cases. It is characterized by insulin resistance, impaired insulin secretion, and hyperglycemia. Lifestyle variables like obesity, sedentary behavior, and poor nutritional choices are frequently linked to type 2 diabetes. Treatment approaches include lifestyle modifications, oral antidiabetic agents, and, in some cases, insulin therapy.[5]

2.2 Gestational Diabetes

Gestational Diabetes occurs during pregnancy when blood glucose levels become elevated. Usually, a diagnosis is made between weeks 24 and 28 of pregnancy. Gestational diabetes increases the risk of complications for both the mother and the baby. Management involves dietary modifications, physical activity, and, in some cases, insulin therapy.[6]

2.3 Other Specific Types

Other Specific Types of diabetes include a diverse group of conditions with distinct aetiologies and clinical characteristics. This category includes monogenic forms of diabetes, such as maturity-onset diabetes of the young (MODY), as well as diabetes resulting from specific genetic syndromes, drug-induced diabetes, and pancreatic diseases.[7]

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3. Pathophysiology of Diabetes

The pathophysiology of diabetes involves a complex interplay of various factors that affect insulin and glucose metabolism, leading to hyperglycemia and the development of diabetic complications. This section discusses the following subheadings: Insulin and Glucose Metabolism, Insulin Resistance, Beta-Cell Dysfunction, and the Role of Inflammation.

3.1 Insulin and Glucose Metabolism

Insulin is a hormone produced by the beta cells of the pancreas and plays a crucial role in regulating glucose metabolism. Insulin is secreted in response to high blood glucose levels following a meal. Insulin promotes the uptake of glucose into cells, stimulates glycogen synthesis in the liver and muscle, and inhibits glucose production by the liver.[8]

3.2 Insulin Resistance

Insulin resistance occurs when cells fail to respond adequately to the action of insulin, resulting in impaired glucose uptake. Adipose tissue, skeletal muscle, and the liver play significant roles in insulin resistance development. Insulin resistance is commonly associated with obesity, physical inactivity, and other metabolic abnormalities, and it is a key characteristic of type 2 diabetes.[9]

3.3 Beta-Cell Dysfunction

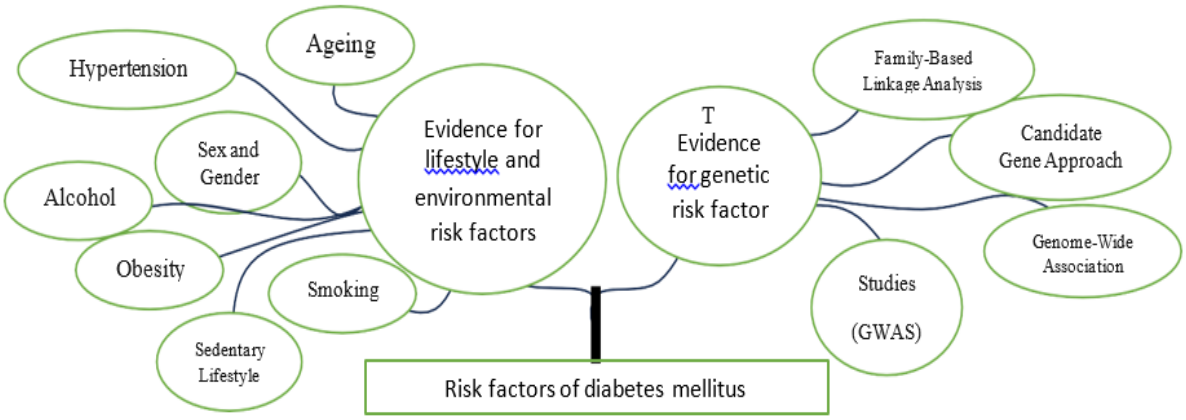
Beta-cell dysfunction refers to impaired insulin secretion by the pancreatic beta cells in response to glucose. In type 2 diabetes, beta-cell dysfunction is characterized by reduced insulin secretion, altered insulin pulsatility, and impaired response to glucose. Over time, beta-cell dysfunction worsens, leading to a progressive decline in insulin production and exacerbation of hyperglycemia.[10]

3.4 Role of Inflammation

Inflammation is involved in the pathogenesis of diabetes, particularly in type 2 diabetes. Chronic low-grade inflammation contributes to insulin resistance and beta-cell dysfunction. Inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6), interfere with insulin signaling pathways and impair beta-cell function, further exacerbating insulin resistance and hyperglycemia.[11]

4. Risk Factors of Diabetes

The etiology of diabetes is multifactorial, involving a combination of genetic, environmental, and lifestyle factors. Understanding these risk factors is crucial for identifying individuals at risk of developing diabetes and implementing preventive measures. This section discusses the following subheadings: Genetic Factors, Environmental Factors, Lifestyle Factors, and Obesity and Diabetes.[12]



4.1 Genetic Factors

Genetic factors play a significant role in the development of diabetes. Certain genes can increase an individual's susceptibility to diabetes by influencing insulin secretion, insulin action, or both. Various genetic variants have been identified, including those associated with type 1 diabetes, type 2 diabetes, and monogenic forms of diabetes.[13]

4.2 Environmental Factors

Environmental factors, such as viral infections, toxins, and early life events, can contribute to the development of diabetes. Viral infections, particularly enteroviruses, have been implicated in the pathogenesis of type 1 diabetes. Exposure to certain toxins, such as chemicals and pollutants, may also increase the risk of developing diabetes.[14]

4.3 Lifestyle Factors

Lifestyle factors, including diet, physical activity, and smoking, significantly impact the risk of developing type 2 diabetes. Unhealthy dietary patterns, such as high intake of refined carbohydrates and saturated fats, along with sedentary behaviour, contribute to insulin resistance and obesity. Smoking has also been associated with an increased risk of type 2 diabetes.[15]

4.4 Obesity and Diabetes

Obesity is a major risk factor for type 2 diabetes. Excess adipose tissue, especially visceral fat, leads to insulin resistance and metabolic dysfunction. Adipose tissue secretes various adipokines and inflammatory mediators, contributing to systemic inflammation and impaired glucose homeostasis. Weight loss and lifestyle modifications are essential in managing and preventing diabetes in individuals with obesity.[16]

5. Acute and Chronic Complications

Diabetes is associated with a range of acute and chronic complications that can significantly impact the health and well- being of individuals with the disease. This section discusses the following subheadings: Acute Complications, including Diabetic Ketoacidosis (DKA), Hyperosmolar Hyperglycemic State (HHS), and Hypoglycemia, as well as Chronic Complications, including Macrovascular Complications and Microvascular Complications.

5.1 Acute Complications

5.1.1 Diabetic Ketoacidosis (DKA)

Diabetic Ketoacidosis is a severe complication that mainly occurs in individuals with type 1 diabetes but can also affect those with type 2 diabetes. It is characterized by hyperglycemia, ketosis, and metabolic acidosis. DKA is often precipitated by factors such as infection, missed insulin doses, or inadequate diabetes management. Prompt medical intervention, including fluid resuscitation and insulin therapy, is crucial to manage DKA.[17]

5.1.2 Hyperosmolar Hyperglycemic State (HHS)

Hyperosmolar Hyperglycemic State, also known as hyperosmolar hyperglycemic nonketotic syndrome (HHNS), is a life-threatening complication typically seen in individuals with type 2 diabetes. It is characterized by severe hyperglycemia, extreme dehydration, and altered mental status. HHS often occurs due to a combination of insulin resistance, relative insulin deficiency, and underlying medical conditions. Immediate medical attention, including fluid replacement and insulin therapy, is essential in managing HHS.[18]

5.1.3 Hypoglycemia

Hypoglycemia refers to a low blood glucose level, typically below 70 mg/dL, and can occur in individuals with diabetes who are using insulin or certain oral antidiabetic medications. Hypoglycemia can lead to various symptoms, including shakiness, confusion, dizziness, and in severe cases, loss of consciousness. Prompt treatment with a fast-acting carbohydrate source, such as glucose tablets or juice, is essential to raise blood sugar levels.[19]

5.2 Chronic Complications

5.2.1 Macrovascular Complications

Macrovascular complications of diabetes are primarily related to the damage of large blood vessels, increasing the risk of cardiovascular diseases. These complications include coronary artery disease, stroke, and peripheral arterial disease. Diabetes management, along with control of blood pressure and cholesterol levels, plays a critical role in reducing the risk of macrovascular complications.[20]

5.2.2 Microvascular Complications

Microvascular complications of diabetes involve damage to small blood vessels, leading to various complications. These complications include diabetic retinopathy (affecting the eyes), diabetic nephropathy (affecting the kidneys), and diabetic neuropathy (affecting the nerves). Strict blood glucose control, blood pressure management, and regular screenings are essential for the prevention and early detection of microvascular complications.[21]

6. Clinical Presentation and Diagnosis

The clinical presentation and diagnosis of diabetes involve recognizing the symptoms, using appropriate diagnostic criteria, implementing screening and prevention strategies, and understanding the potential complications of late diagnosis. This section discusses the following subheadings: Symptoms and Signs, Diagnostic Criteria, Screening and Prevention Strategies, and Complications of Late Diagnosis.

6.1 Symptoms and Signs

The symptoms and signs of diabetes can vary depending on the type of diabetes and the severity of the disease. Common symptoms include increased thirst, frequent urination, unexplained weight loss, fatigue, blurred vision, and slow wound healing. In type 1 diabetes, symptoms can develop rapidly, while in type 2 diabetes, they may be subtle and progress gradually.[22]

6.2 Diagnostic Criteria

Diagnostic criteria for diabetes are established to identify individuals with elevated blood glucose levels indicative of the disease. The criteria differ for type 1 and type 2 diabetes. The American Diabetes Association (ADA) and the World Health Organization (WHO) provide guidelines for diagnosing diabetes based on fasting plasma glucose levels, oral glucose tolerance tests, and HbA1c levels.[23]

6.3 Screening and Prevention Strategies

Screening and prevention strategies aim to identify individuals at risk of developing diabetes and intervene to prevent or delay its onset. Screening is recommended for individuals with risk factors, such as obesity, family history of diabetes, or history of gestational diabetes. Prevention strategies involve lifestyle modifications, including healthy eating, regular physical activity, weight management, and smoking cessation.[24]

6.4 Complications of Late Diagnosis

Late diagnosis of diabetes can lead to a higher risk of complications due to uncontrolled hyperglycemia over an extended period. Complications may include cardiovascular diseases, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, and diabetic foot ulcers. Early diagnosis and prompt initiation of appropriate treatment are essential to minimize the risk of complications.[25]

7. Management Strategies

Effective management of diabetes involves a comprehensive approach that includes lifestyle modifications, pharmacological interventions, insulin therapy, patient education and support, and emerging treatment approaches. This section discusses the following subheadings: Lifestyle Modifications, Pharmacological Interventions, Insulin Therapy, Patient Education and Support, and Emerging Treatment Approaches.

7.1 Lifestyle Modifications

Lifestyle modifications form the foundation of diabetes management. They include dietary changes, regular physical activity, weight management, and smoking cessation. A balanced diet rich in fruits, vegetables, whole grains, lean proteins, and healthy fats is recommended. Engaging in regular physical activity, such as aerobic exercises and strength training, helps improve insulin sensitivity. Weight management and smoking cessation are crucial in reducing the risk of complications.[26]

7.2 Pharmacological Interventions

Pharmacological interventions are essential in the management of diabetes, particularly when lifestyle modifications alone are insufficient to achieve glycemic control. Oral antidiabetic agents, such as metformin, sulfonylureas, and DPP-4 inhibitors, are commonly prescribed. In some cases, injectable medications like GLP-1 receptor agonists and SGLT-2 inhibitors may be used. The choice of medication depends on individual factors and disease characteristics.[27]

7.3 Insulin Therapy

Insulin therapy is crucial in individuals with type 1 diabetes and may also be required for some individuals with type 2 diabetes. Insulin is administered through injections or insulin pumps to replace or supplement endogenous insulin production. Various types of insulin, such as rapid-acting, short-acting, intermediate- acting, and long-acting insulins, are available to meet individual needs. Insulin therapy aims to achieve and maintain target blood glucose levels.[28]

7.4 Patient Education and Support

Patient education and support are vital components of diabetes management. Education helps individuals understand the disease, learn self-management skills, and make informed decisions about their care. It includes topics such as blood glucose monitoring, medication adherence, healthy eating, and sick day management. Support from healthcare professionals, diabetes educators, and peer support groups plays a crucial role in empowering individuals to manage their condition effectively.[29]

7.5 Emerging Treatment Approaches

Emerging treatment approaches in diabetes management aim to provide additional therapeutic options for improved glycemic control and prevention of complications. These may include novel medications, such as selective PPAR modulators and glucokinase activators, as well as advancements in technology, such as closed-loop insulin delivery systems and artificial pancreas. Ongoing research and development efforts continue to explore innovative approaches to diabetes management.[30]

8. Prevention and Public Health Initiatives

Prevention and public health initiatives play a crucial role in reducing the burden of diabetes by focusing on primary prevention to prevent the onset of diabetes and secondary prevention to mitigate complications in individuals already diagnosed with the disease. Additionally, national and global initiatives aim to address the challenges of diabetes on a broader scale. This section discusses the following subheadings: Primary Prevention, Secondary Prevention, and National and Global Initiatives.

8.1 Primary Prevention

Primary prevention strategies aim to reduce the risk of developing diabetes in individuals who are currently free from the disease. These strategies primarily focus on promoting healthy lifestyle behaviors, such as maintaining a balanced diet, engaging in regular physical activity, and achieving and maintaining a healthy body weight. Public health campaigns, educational programs, and community interventions are implemented to raise awareness and provide resources for prevention.[31]

8.2 Secondary Prevention

Secondary prevention strategies focus on early detection and management of diabetes to prevent or delay the progression of complications. These strategies involve regular screening for complications, such as diabetic retinopathy, nephropathy, and neuropathy, and implementing interventions to manage blood glucose levels, blood pressure, and lipid levels. Collaborative care models involving healthcare professionals, diabetes educators, and multidisciplinary teams are often employed for effective secondary prevention.[32]

9. Pharmacological Interventions

All psychological interventions were pooled together, analyses of heterogeneity, and considered this when adjudicating the strength of evidence. The mode of delivery was defined as an individual, group, or family therapy carried out in whole or in part by a healthcare professional. The comparison group was defined as consistent with a similar review of type 1 diabetes interventions (Winkley, 2020): 'no intervention', 'usual care, 'wait-list control', 'attention control', or 'clinical management (CM). Regarding differential or incremental effects of different treatment approaches, trials were considered with a control group receiving pharmacological treatment or another psychological treatment. Any medication provided for the primary purpose of preventing the onset of diabetes was included. Also included were studies that combined pharmacotherapy with other diabetes preventive strategies, including educational, behavioural, surgical interventions, or lifestyle (diet and exercise). Included were both medicine and over-the-counter drugs.[33]

9.1 Insulin therapy

Among adults with type 2 diabetes, initiation of insulin is often delayed beyond clinical need. However, many adults with type2 diabetes decline insulin therapy upon prescription, and individuals' willingness to start insulin contributes significantly to the prediction of timely insulin initiation, independent of the model of care received. Hesitancy to initiate insulin therapy, sometimes referred to as 'psychological insulin resistance 'is based on negative attitudes, or beliefs, about insulin, including perceiving insulin as unnecessary or ineffective, concerns about insulin side effects, physical and social impacts, as well as what insulin represents (symbolically) for health and identity.5, In response, collaborative consultation strategies are recommended, with injection demonstrations, explanation of treatment benefits, and discussion of concerns about insulin having been retrospectively reported as facilitators of insulin initiation. Scalable and accessible interventions (external from, or supplementary to, clinical care) may provide an opportunity to address individuals' concerns about insulin while minimizing the burden on healthcare resources. [34] Intensive insulin therapy is a strategy used to reduce hyperglycemia and by extension mitigate cardiovascular disease development in patients with T1D. Insulin resistance is characterized by an inefficient biological response to circulating insulin and has been shown to occur in the presence of Type 1 Diabetes (T1D). Regular exercise has been shown to reduce indices of insulin resistance. However, a primary limitation to participation in regular exercise among individuals with T1D is a risk of exercise-induced hypoglycemia and this risk may be enhanced by intensive insulin treatment.[35]

9.2 Oral Antidiabetic Agents

Oral antidiabetic agents are an essential component of diabetes management, particularly for individuals with type 2 diabetes. They work by various mechanisms to improve glycemic control and reduce the risk of complications. This section will discuss the following subheadings: metformin, SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors.

9.2.1 Metformin

Metformin is considered the first-line oral antidiabetic agent for type 2 diabetes due to its efficacy, safety profile, and beneficial effects beyond glycemic control. It primarily acts by reducing hepatic glucose production and enhancing insulin sensitivity in peripheral tissues. Metformin is also associated with weight neutrality or modest weight loss. It has been shown to reduce cardiovascular events and mortality in patients with diabetes.[36] Glycemic control in T2DM care is individualized. Depending on the age, concurrent conditions and treatment history, the A1c level may be set at a different target. T2DM is a progressive chronic condition, patients generally require eventual treatment intensification (TI) to maintain adequate A1c control. The ADA recommends a stepwise approach to TI starting with metformin monotherapy in patients with T2DM other therapies are then added on if intensification is required, and may ultimately be combined with or changed to injectable options, including insulin, if the A1c target is not achieved. Multiple studies have shown that for patients who were not responsive to the metformin-based treatment, the faster patients intensify their treatment to meet therapy goals, the bigger the impact it will be.[37]

9.2.2 SGLT-2 Inhibitors

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a newer class of oral antidiabetic agents that work by blocking the reabsorption of glucose in the kidneys, leading to increased urinary glucose excretion. This mechanism results in improved glycemic control, weight loss, and blood pressure reduction. SGLT-2 inhibitors have also demonstrated cardiovascular and renal benefits, making them an attractive option for patients with diabetes and cardiovascular comorbidities.[38]

9.2.3 GLP-1 Receptor Agonists

GLP-1 receptor agonists are injectable medications that mimic the action of glucagon-like peptide-1 (GLP-1), a hormone that

enhances glucose-dependent insulin secretion, suppresses glucagon release, slows gastric emptying, and promotes satiety. GLP-1 receptor agonists are associated with improved glycemic control, weight loss, and cardiovascular benefits. They are available in different formulations, including once-daily and once-weekly injectables.[39]

9.2.4 DPP-4 Inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors work by inhibiting the enzyme responsible for the degradation of incretin hormones, such as GLP-1. By prolonging the action of incretin hormones, DPP-4 inhibitors increase insulin secretion and decrease glucagon release in a glucose-dependent manner. These agents have shown efficacy in lowering blood glucose levels with a low risk of hypoglycemia. They are available in oral formulations and are generally well-tolerated.[40]

9.3 Emerging Therapies

9.3.1 Dual and Triple Combination Therapies

Dual and triple combination therapies involve the use of two or three different classes of antidiabetic agents to achieve better glycemic control in patients with diabetes. These emerging therapies aim to address the complex pathophysiology of diabetes by targeting multiple pathways simultaneously. By combining agents with complementary mechanisms of action, they offer the potential for improved efficacy, convenience, and tolerability.[41]

9.3.2 Novel Insulin Formulations

Novel insulin formulations aim to improve insulin delivery and optimize glycemic control in patients with diabetes. These formulations may include ultra-rapid-acting insulins, which have a faster onset of action and shorter duration compared to traditional rapid-acting insulins. Additionally, long-acting insulins with prolonged duration and improved stability may provide more consistent basal insulin coverage.[42]

9.3.3 Gene Therapy

Gene therapy holds promise as an emerging therapeutic approach for diabetes by targeting the underlying genetic factors contributing to the disease. It involves the introduction of genes that enhance insulin production, improve insulin sensitivity, or modulate glucose metabolism. Although still in the experimental stage, gene therapy has the potential to provide long-term benefits and transform the treatment landscape for diabetes.[43]

9.3.4 Artificial Pancreas Systems

Artificial pancreas systems, also known as closed-loop systems, combine continuous glucose monitoring (CGM) technology with automated insulin delivery to mimic the function of a healthy pancreas. These systems use algorithms to adjust insulin infusion rates based on real-time glucose measurements, providing more precise glycemic control and reducing the risk of hypoglycemia.[44]

10. Pharmacist's Role in Patient-centred Diabetes Care

Pharmacists play a vital role in providing patient-centred care for individuals with diabetes. Their expertise in medication management, counselling, and education helps optimize therapeutic outcomes and improve patients' overall health and well-being. This section discusses the following subheadings: Medication Therapy Management (MTM), Collaborative Care Models, Patient Education and Counselling, and Shared Decision Making.

10.1 Medication Therapy Management (MTM)

Medication Therapy Management (MTM) involves comprehensive medication reviews, assessment of therapy adherence, identification and resolution of medication-related problems, and patient education. Pharmacists, through MTM services, ensure appropriate medication selection, dosing, and monitoring to achieve optimal glycemic control and minimize medication-related complications.[45]

10.2 Collaborative Care Models

Collaborative care models involve pharmacists working closely with other healthcare providers, such as physicians, nurses, and

dietitians, to provide integrated and coordinated diabetes care. These models facilitate interprofessional collaboration, allowing pharmacists to contribute their expertise in medication management, monitoring, and patient education within a collaborative healthcare team.[46]

10.3 Patient Education and Counselling

Pharmacists play a crucial role in educating patients about diabetes self-management, including medication use, lifestyle modifications, blood glucose monitoring, and recognition of symptoms. They provide counseling to promote medication adherence, healthy eating habits, regular physical activity, and proper use of medical devices, such as glucose meters and insulin pens.[47]

10.4 Shared Decision Making

Shared decision-making involves pharmacists and patients collaborating to make informed decisions about treatment options, taking into account the patient's preferences, values, and goals. Pharmacists provide evidence-based information, clarify treatment choices, and engage patients in discussions regarding the benefits, risks, and potential outcomes of different therapeutic interventions.[48]

11. Emerging Technologies in Diabetes Management

11.1 Continuous Glucose Monitoring (CGM)

Continuous Glucose Monitoring (CGM) systems provide real- time or near real-time measurements of glucose levels, allowing individuals with diabetes to monitor their blood glucose trends throughout the day. CGM devices consist of a sensor placed under the skin that measures interstitial glucose levels and transmits the data to a receiver or smartphone. CGM technology has the potential to improve glycemic control, reduce hypoglycemia, and enhance patient self-management.[49]

11.2 Telehealth and Digital Health Interventions

Telehealth and digital health interventions leverage technology to facilitate remote healthcare delivery, monitoring, and support for individuals with diabetes. These interventions include virtual consultations, remote monitoring of vital signs and glucose levels, and web-based educational programs. Telehealth and digital health interventions offer convenience, accessibility, and personalized care, enabling patients to receive timely support and guidance from healthcare professionals.[50]

11.3 Mobile Applications and Self-Management Tools

Mobile applications and self-management tools provide individuals with diabetes access to personalized tools and resources for self-monitoring, medication adherence, meal planning, physical activity tracking, and glucose trend analysis. These tools empower patients to actively participate in their diabetes management and facilitate self-care behaviours, leading to improved self-efficacy and better treatment outcomes.[51]

11.4 Artificial Intelligence and Machine Learning

Artificial Intelligence (AI) and Machine Learning (ML) technologies have the potential to revolutionize diabetes management by analysing large datasets, predicting individualized treatment responses, and providing decision support to healthcare professionals. AI and ML algorithms can assist in insulin dosing recommendations, early detection of complications, and personalized risk assessment, thereby improving patient outcomes and healthcare efficiency.[52]

12. Pharmacist-Led Diabetes Prevention Programs

Pharmacists play a vital role in diabetes prevention through their expertise in medication management, patient education, and healthcare accessibility. Pharmacist-led diabetes prevention programs focus on empowering individuals to make positive lifestyle modifications, providing risk assessment and screening services, delivering diabetes prevention education, and engaging with the community through outreach efforts. This section discusses the following subheadings: Lifestyle Modifications and Behaviour Change, Risk Assessment and Screening, Diabetes Prevention Education, and Community Engagement and Outreach.

12.1 Lifestyle Modifications and Behaviour Change

Pharmacist-led diabetes prevention programs emphasize the importance of lifestyle modifications and behaviour change in

preventing the onset of diabetes. Pharmacists provide personalized counselling and guidance to individuals on adopting healthy eating habits, increasing physical activity, managing stress, and improving sleep patterns. They support behaviour change by setting realistic goals, monitoring progress, and providing ongoing motivation and support.[53]

12.2 Risk Assessment and Screening

Pharmacists are trained to conduct risk assessments and screenings to identify individuals at high risk of developing diabetes. They use validated tools and techniques to assess risk factors such as family history, obesity, sedentary lifestyle, and abnormal glucose levels. By identifying individuals at risk, pharmacists can initiate appropriate interventions and refer them to healthcare providers for further evaluation and management.[54]

12.3 Diabetes Prevention Education

Pharmacists play a crucial role in providing diabetes prevention education to individuals at risk. They educate patients about the importance of early detection, lifestyle modifications, and the role of medications, if necessary. Pharmacists also provide information on self-monitoring techniques, such as blood glucose monitoring, and educate patients on recognizing and managing signs of hyperglycemia and hypoglycemia. Patient education empowers individuals to take control of their health and make informed decisions.[55]

12.4 Community Engagement and Outreach

Pharmacists actively engage with the community to raise awareness about diabetes prevention and promote healthy behaviours. They collaborate with local organizations, schools, workplaces, and community centres to provide educational sessions, health screenings, and counselling services. Pharmacists participate in health fairs, community events, and support groups to reach a broader audience and provide resources for diabetes prevention.[56]

13. Interprofessional Collaboration in Diabetes Care

Interprofessional collaboration is crucial in diabetes care as it involves a multidisciplinary approach that brings together healthcare professionals from various disciplines to provide comprehensive and coordinated care to individuals with diabetes. Interprofessional collaboration facilitates improved patient outcomes, enhances patient satisfaction, and optimizes healthcare delivery. This section discusses the following subheadings: Team-Based Approaches, Collaborative Care Networks, Integrated Electronic Health Records, and Communication and Care Transitions.

13.1 Team-Based Approaches

Team-based approaches involve the collaboration of healthcare professionals, such as physicians, nurses, pharmacists, dietitians, and diabetes educators, working together to provide holistic care for individuals with diabetes. Each team member contributes their unique expertise and perspective to develop and implement personalized care plans, monitor progress, and address the various aspects of diabetes management. Team- based approaches enhance patient-centered care, promote shared decision-making, and improve treatment outcomes.[57]

13.2 Collaborative Care Networks

Collaborative care networks involve establishing partnerships and networks between healthcare organizations, community resources, and other stakeholders involved in diabetes care. These networks facilitate communication, coordination, and information sharing among healthcare providers, enabling seamless transitions of care and promoting continuity. Collaborative care networks also enhance access to specialized care, improve care coordination, and facilitate the integration of services across different healthcare settings.[58]

13.3 Integrated Electronic Health Records

Integrated electronic health records (EHRs) enable seamless communication and information sharing among healthcare professionals involved in diabetes care. EHRs provide a centralized platform for storing and accessing patient information, including medical history, laboratory results, medication records, and care plans. This integration enhances care coordination, reduces duplication of efforts, and promotes continuity of care. Healthcare providers can access real-time patient data, make informed decisions, and collaborate effectively within the interprofessional team.[59]

13.4 Communication and Care Transitions

Effective communication and care transitions are vital in interprofessional collaboration for diabetes care. Clear and timely communication among healthcare providers ensures that important information is shared, treatment plans are coordinated, and patient needs are addressed. Care transitions, such as hospital discharges or referrals to specialists, require seamless transfer of information to ensure continuity of care. Communication tools, such as standardized handover protocols and electronic communication systems, facilitate effective communication and enhance patient safety.[60]

14. Future Directions and Challenges

The future of diabetes care is characterized by ongoing advancements and challenges that require attention and strategic planning. This section discusses the following subheadings: Precision Medicine in Diabetes Management, Health Equity and Access to Care, Regulatory and Policy Considerations, and Research and Evidence-Based Practice.

14.1 Precision Medicine in Diabetes Management

Precision medicine aims to tailor medical interventions and treatment strategies to individual patients based on their unique genetic, environmental, and lifestyle factors. In diabetes management, precision medicine involves identifying biomarkers, genetic variants, and other patient-specific characteristics that influence disease progression and response to treatment. Utilizing precision medicine approaches can lead to more targeted and personalized interventions, improved treatment outcomes, and enhanced patient satisfaction.[61]

14.2 Health Equity and Access to Care

Ensuring health equity and improving access to diabetes care is a significant challenge. Disparities in healthcare access, socioeconomic factors, and cultural barriers can contribute to unequal health outcomes among individuals with diabetes. Future directions in diabetes care involve addressing these disparities through targeted interventions, community engagement, and policy changes. Strategies include increasing healthcare access, providing culturally competent care, and implementing programs to reach underserved populations.[62]

14.3 Regulatory and Policy Considerations

Regulatory and policy considerations shape the landscape of diabetes care. Future directions involve establishing regulations and policies that promote quality care, patient safety, and innovation. This includes ensuring access to affordable medications, encouraging reimbursement for comprehensive diabetes care services, and implementing guidelines and standards that align with evidence-based practices. Regulatory and policy frameworks should support collaborative care models, interprofessional collaboration, and patient-centered approaches.[63]

14.4 Research and Evidence-Based Practice

Research and evidence-based practice are essential for advancing diabetes care. Future directions involve continued research efforts to enhance our understanding of the pathophysiology, prevention, and treatment of diabetes. This includes conducting clinical trials, genetic studies, and translational research to identify novel interventions and therapeutic targets. Furthermore, promoting the adoption of evidence-based guidelines and practices in clinical settings is crucial for optimizing patient outcomes and ensuring quality care.[64]

15. Diabetes Prediction

15.1 Using Ensemble of Different Machine Learning Classifiers

Research on diabetes patients demonstrates that diabetes among adults (over 18 years old) has risen from 4.7 % to 8.5 % from 1980 to 2014 respectively and rapidly growing in second and third-world countries. Statistical results in 2017 show that 451 million people were living with diabetes worldwide, which will increase to 693 million by 2045. Another statistical study shows the severity of diabetes, where they reported that half a billion people have diabetes worldwide, and the number will increase to 25 % and 51 % respectively in 2030 and 2045. However, there is no long-term cure for diabetes, but it can be controlled and prevented if an early prediction is accurately possible. The prediction of diabetes is a challenging task. Numerous strategies for diabetes prediction have been put out and published in recent years. The robust and accurate prediction of diabetes is highly challenging due to the limited

number of labeled data and also the presence of outliers (or missing values) in the diabetes datasets. In this literature, we propose a robust framework for diabetes prediction using different Machine Learning (ML) classifiers (k-nearest Neighbour, Decision Trees, Random Forest, AdaBoost, Naive Bayes, and XGBoost) and Multilayer Perceptron (MLP). This framework includes features such as outlier rejection, data standardization, feature selection, K-fold cross-validation, and feature selection. [65]

15.2 Classification Algorithms

Finding diabetes at an early stage is one of the major medical issues that exist in real life. In many studies, systematic efforts are made to design a system that results in the prediction of diseases like diabetes. To identify diabetes at an early stage, this experiment employs three machine learning classification algorithms: Decision Tree, SVM, and Naive Bayes. Experiments are performed on the Pima Indians Diabetes Database. Experimental results determine the adequacy of the designed system with an achieved accuracy of 76.30 % using the Naive Bayes classification algorithm. Future research may involve the prediction or diagnosis of other diseases using the developed system and the machine learning classification methods. Other machine learning algorithms can be added to the work to improve and expand it for the automation of diabetes analysis. [66]

15.3 Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045

2019 diabetes prevalence is predicted to reach 463 million individuals (95% confidence interval: 369-601 million). The necessity for creating and executing multi-sectoral strategies to combat diabetes is important given that there are 500 million individuals worldwide who have the disease. It is estimated that 578 million people will have diabetes in 2030 and that figure will rise by 51% (700 million) in 2045 if prompt and effective measures are not taken. [67]

16. Impact Of Diabetes

16.1 Economic Impact of Diabetes

Diabetes economically shows the impact on individual persons, their families, the health system, and the economy of the nation. Diabetes shows long-term economic impact on diabetes patient and their families. [4] Diabetes is a financial burden on individuals. The cost of care for diabetes affects patients. The cost of care for diabetes is classified into three types- Direct cost, Indirect cost, and Intangible cost. Direct cost means medical costs, household expenses, and hospital service costs. Indirect cost means loss of resources, absenteeism, and presentism. Intangible cost means changes in the daily life of the patient and their families. [68]

16.2 Impact of diabetes in daily life

Diabetes affects many facet of patient and their family such as mental health, professional life, driving issue, sexual problem and pregnancy problem. Mental health means diabetes affects the patient psychologically because they feel that diabetes cause problem in their works. Diabetes patient feel discriminated at their work place. Many countries such as UK does not issue driving license to diabetes patient which cause driving issue to patient. There is a risk of death of babies of pregnant woman who has diabetes. [69]

17. Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials

In order to verify the use of time in range (TIR) as an outcome measure for clinical studies, the relationship between TIR of 3.9–10 mmol/L and the onset or progression of retinopathy and the onset of microalbuminuria was examined. TIR should be included as a viable end point in clinical studies since it has a high correlation with the risk of microvascular problems. TIR and other glycaemic metrics, particularly when evaluated with continuous glucose monitoring, provide value as outcome measures in many studies even if haemoglobin A1c continues to be a useful outcome metric in therapeutic trials. [70]

18. Diabetes and COVID-19

A recently discovered ailment known as COVID-19 has been quickly spreading throughout China and the rest of the world since the end of 2019. A novel beta-coronavirus, known as the severe acute respiratory syndrome corona virus 2 (SARS-CoV- 2), was identified as the COVID-19 pathogen, which triggered severe pneumonia and acute, even lethal, lung failure. Diabetes with greater weight loss and greater pulmonary inflammation, with macrophage infiltrates similar to those seen clinically in the disease. As with influenza-related mortality, diabetes is a significant risk factor for unfavourable results, regardless of the propensity for COVID-19 to spread. One of the comorbidities linked to the morbidity and mortality of 509 COVID-19 is diabetes. Individuals with diabetes may be at increased risk for COVID-19 severity due to a combination of underlying chronic conditions like hypertension, obesity, and cardiovascular diseases, as well as altered ACE2 receptor expression, immune 511 dysregulations, alveolar and endothelial dysfunction, and increased systemic coagulation. People with pre-existing diabetes have experienced significant changes in their

quality of life as a result of the COVID19 pandemic and the subsequent policy responses, such as lockdowns. The COVID-19 pandemic, in our opinion, is a watershed event in the history of epidemiology, and diabetes epidemiology should be a major player. As opposed to COVID-19 patients with known diabetes, hyperglycaemia, and normal glucose levels, we first demonstrated that COVID-19 patients with recently diagnosed diabetes had the highest risk of all-cause death. Blood glucose testing requires close monitoring of patients who have COVID-[71] [72] [73] [74] [75][76].

Conclusion:

Diabetes mellitus, which is becoming more common due to aging populations, urbanization, and changing lifestyles, is still a major global health concern. Type 1 and Type 2 diabetes are the two most frequent forms of the disease, but there are other, les s common types as well, such as gestational and monogenic diabetes. Diabetes is a complex illness with several etiologies. Diabetes is a complex pathophysiology that includes both environ mental and hereditary components, emphasizing the necessity f or individualized treatment plans and the disease's multifactorial character. Significant advancements in treatment possibilities have been prompted by recent progress in understanding the mechanisms underlying diabetes. Newer pharmacological treatments, like SGLT2 inhibitors and GLP1 receptor agonists, have developed as alternatives to standard insulin therapy, providing better glycemic control, weight management, and cardiovascular protection. Technology advancements are revolutionizing diabetes care by making it possible to monitor and regulate blood glucose levels more precisely. In particular, continuous glucose monitoring devices and insulin pumps are making this possible. The quality of life and patient outcomes are being enhanced by these advancements, particularly for patients with Type 1 diabetes. However, despite these advances, he long-term complications of diabetes, including microvascular and macrovascular issues, continue to pose a substantial burden on individuals and healthcare systems. Early diagnosis, lifestyle modifications, and vigilant management remain cornerstones in preventing or delaying these complications. Future studies should concentrate on enhancing current treatments, advancing early detection techniques, and creating fresh, more potent approaches to diabetes treatment and prevention. To aid in the creation of focused treatments, more attention needs to be paid to comprehending the molecular causes of diabetes. In conclusion, advances in technology and medicine represent a promising avenue for improved outcomes in the critical field of diabetes care. In order to overcome the continued challenges fac ed by this disease and lessen its global impact, multidisciplinary teamwork must continue.

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