Comprehensive Review of Pharmacological Therapies and Clinical Guidelines for Diabetes Mellitus: A Depth Study

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Abstract

Diabetes mellitus (DM) is a colossal burden in global health, its prevalence increases steadily throughout the world. This systematic review explores the pathophysiology and epidemiology of diabetes, which describes the interactions that implicate that is the result of the play between genetic, environmental, and lifestyle factors in the development and progression of the disease. The review also describes a plethora of pharmacological treatments available to manage diabetes, with the oral agent, insulin regimens, and new approaches to therapy. Integrating the wisdom of the best clinical guidelines, those are from American diabetes association (ADA), European association for the study of diabetes (EASD), and International Diabetes Federation (IDF). Since these reviews are consistent with normative standards for evidence-based recommendations of optimal care of diabetes. The review goes further to cover technological advances in the management of diabetes. They include Continuous Glucose Monitoring, advanced insulin delivery systems, and Artificial Pancreas Systems. Such technologies hold more promising routes to better glucose control and patient quality of life. All this comes along with challenges that their deployment and maintenance that run through economic, adherence issues, and unequal access to healthcare. The future research and innovation in the battle against

DM will include the application of personalized medicine and the development of advanced digital health solutions. This article will become a treasure for health professionals, researchers, and policymakers who have dedicated themselves to battling the adversities of diabetes mellitus.

Keywords: Diabetes mellitus, Pathophysiology, Clinical guidelines, Pharmacological treatment, Technology.

1. Introduction

Diabetes Mellitus (DM) is one of the global health problems that continue to escalate due to its sustained hyperglycemia caused by insufficient insulin secretion and/or reduced utilization by the body cells. As a result of this increasing global prevalence, it is crucial to understand and manage DM with improved drug treatment methods and clinical adherence. This paper aims to exhaustively cover current pharmacotherapeutic options for diabetes, assess contemporary clinical guidelines, and discuss technological advancements that are revolutionizing diabetes care (F. Sugandh et al., 2023).

A. Background on Diabetes Mellitus (DM)

DM refers to a broad class of metabolic disorders characterized mainly by the presence of chronic hyperglycemia that can be attributed to a wide variety of abnormalities in insulin secretion and/or action. The disease appears in various forms, like T1DM, T2DM, and gestational diabetes, depending on etiological factors and therapeutics strategies implemented. ("Diagnosis and classification of diabetes mellitus," 2009). T1DM usually occurs in children or adolescents who have destroyed their own pancreatic beta cells through an autoimmune process thus making them unable to produce any insulin. This results in a complete deficiency of insulin. The pathogenesis of T1DM is influenced by genetic factors and environmental triggers that initiate the autoimmune reaction (Popoviciu et al., 2023). On the other hand, T2DM is more common and usually becomes manifested in adults, though the number of this disease among children is rising. This kind of diabetes is mainly characterized by low levels of insulin with relatively a certain level of resistance to its action; these conditions may be worsened by such elements as obesity, lack of physical exercise, and poor dietary habits (Galicia-Garcia et al., 2020). Gestational Diabetes is a type that happens to pregnant women when the level of blood sugar rises because the body is resistant to insulin just as people suffering from type 2 diabetes mellitus. Diagnosis with GD raises one's risk of having type 2 diabetes later in life (Plows et al., 2018). If left uncontrolled, it might create long-term complications that can be severe, from heart disease to damage to the nerve which eventually causes loss of sensation or numbness in the affected parts, such as the feet, renal failure, where the wastes accumulate abnormally because the kidneys cannot filter them normally, thereby causing major complications within body systems, and blindness which highly increase the chances of death among individuals living with this disease.

B. Significance of Advances in DM Management

Global public health is greatly affected by advancements in DM management. As DM incidence spreads and escalates to epidemic proportions across the world, new therapeutic methods become of great importance to reduce the burden of the disease and its complications. Such developments assist not only in the control of blood glucose level but also in a reduction in opportunities for severe consequences, including macrovascular and microvascular complications (Aloke et al., 2022). Not only do recent advances optimize glycemic control but they also mitigate against bad sequelae which include macrovascular and microvascular diseases. Novel pharmacotherapeutic agents coupled with technology such as continuous glucose monitoring systems and more advanced modes of insulin delivery offer people suffering from diabetes mellitus never before seen opportunities for individualized precise treatment (Ceriello et al., 2022). Moreover, these improvements act as drivers towards personalized therapeutic regimens that match treatment strategies with each patient's unique phenotypic and metabolic qualities. As ongoing research endeavors persist in elucidating the complex pathophysiological mechanisms underlying DM, the importance of these breakthroughs is poised to increase significantly (Tiwari, 2015). This trajectory promises to foster a paradigmatic evolution towards more efficacious and patient-centric management strategies for this prevalent metabolic disorder.

2. Overview of Diabetes Mellitus

A. Classification and Epidemiology

Diabetes mellitus is a metabolic disorder whereby the inability of the body to produce any or sufficient amount of insulin leads to excessive amounts of glucose in the blood. The manifestation of T1D is usually in childhood or adolescence and characterized by autoimmune destruction of β-cells leading to absolute deficiency of insulin, while T2D results mainly during adulthood due to combinations of factors that include insulin resistance in peripheral tissues and insufficient secretion of insulin by pancreatic β-cells. Gestational diabetes results from hormone resistance to insulin action during pregnancy; different subtypes also exist from various genetic abnormalities and exposure to environmental stimuli that evoke immunity reactions to drugs ("Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022," 2022).

DM has become one of the most significant public health problems worldwide: according to recent estimates, about 537 million adults were living with diabetes across the globe in 2021; this number is expected to rise until 643 million people will have it by 2030 thus demanding immediate preventive measures along with integrated care management programs. The prevalence rates for DM are influenced by urbanisation process which promotes physical inactivity coupled with unhealthy eating habits marked by high intake levels on processed foods rich in calories as well as growing numbers elderly individuals. Moreover, disparities in DM prevalence and outcomes manifest along demographic and socio-economic lines, disproportionately impacting marginalized populations and individuals with limited healthcare access (Saeedi et al., 2019). A nuanced understanding of the multifaceted classifications and epidemiological dynamics of DM is paramount for devising targeted interventions, optimizing resource allocation, and implementing population-wide initiatives to curb this burgeoning public

health challenge. Furthermore, ongoing exploration into the genetic, environmental, and lifestyle determinants of DM holds promise for identifying novel therapeutic targets and preventive avenues, offering prospects for mitigating the escalating burden of this pervasive metabolic disorder.

B. Pathophysiology of DM

The aetiology of DM involves numerous genetic, environmental and lifestyle factors that cause the abnormality of glucose control and long-term hyperglycemia. In T1DM, insulin deficiency occurs due to the destruction of pancreatic beta cells by an autoimmune process. This begins when genetically susceptible individuals are exposed to certain viruses or influenced by their diets which activate autoantibodies against islet cells in the pancreas. Consequently, there is inadequate production of insulin leading to the need for exogenous administration for control of blood sugar levels (Roep et al., 2021).

However, T2DM arises mainly from resistance towards insulin action at peripheral tissues characterized by decreased sensitivity. At first, this is compensated for through increased secretion thus maintaining normal blood sugar; nevertheless, with time there is more failure on part of beta cells resulting into diminished amounts being released thereby worsening hyperglycemia. Causes of insulin resistance encompass obesity, chronic inflammation associated with dysfunctional adipose tissue as well as genetic predisposition among others too. Furthermore, abnormality in release pattern of adipokines altered signaling for gut hormones alongside storage fats at wrong sites all combine to disrupt further homeostasis of carbohydrates metabolism through aggravation metabolic dysfunction induced by such interference which leads insulin resistance (Galicia-Garcia et al., 2020).

Chronic hyperglycemia in diabetes promotes systemic oxidative stress, inflammation, and endothelial dysfunction, resulting in microvascular and macrovascular consequences. Oxidative stress-mediated beta cell damage contributes to decreased insulin production, continuing the hyperglycemic loop. Furthermore, dyslipidemia and systemic inflammation lead to accelerated atherosclerosis and elevated cardiovascular risk in DM patients (Fiorentino et al., 2013). A thorough knowledge of DM's complex pathophysiological pathways is required to guide tailored therapy therapies and prevention initiatives. Ongoing research efforts are elucidating the complicated molecular pathways involved in DM development, presenting exciting opportunities for developing innovative treatment approaches and personalised medicine tailored to specific patient profiles.

C. Impact on Health and Healthcare Systems-

DM exerts a profound influence on both individual health outcomes and healthcare systems globally, presenting complex challenges throughout the care continuum. At the individual level, DM is linked to an array of acute and chronic complications, including cardiovascular disease, nephropathy, neuropathy, retinopathy, and diabetic foot ulcers (Leon & Maddox, 2015). These complications not only degrade the quality of life but also contribute to heightened morbidity and mortality rates among affected individuals. Additionally, managing DM requires strict glycaemic control, frequent blood glucose monitoring, adherence to intricate treatment

protocols, and lifestyle adjustments, imposing significant physical, emotional, and financial burdens on patients and their caregivers.

On a broader spectrum, DM places a substantial strain on healthcare systems, entailing substantial healthcare expenditures and resource utilization. Direct medical costs associated with DM management encompass expenses related to medications, medical consultations, hospitalizations, and diagnostic tests. Moreover, indirect costs stemming from disability, decreased productivity, and premature mortality further amplify the economic impact of DM on society. Furthermore, the increasing prevalence of DM leads to heightened demand for healthcare services, placing added pressure on healthcare infrastructure and exacerbating healthcare inequalities, particularly in resource-constrained settings (Simeone et al., 2020).

Tackling the multifaceted challenges posed by DM necessitates a comprehensive, interdisciplinary approach encompassing preventive strategies, early detection, patient education, and evidence-based therapeutic interventions. Effective diabetes management initiatives should prioritize population-wide endeavors aimed at promoting healthy behaviors, mitigating modifiable risk factors, and facilitating early identification of prediabetes and undiagnosed diabetes through screening endeavours (Jyotsna et al., 2023). Furthermore, optimizing healthcare delivery models to facilitate integrated, coordinated, and patient-centric care is essential for enhancing clinical outcomes, improving patient satisfaction, and containing healthcare expenditures associated with DM management. Through the implementation of integrated and innovative tactics tailored to the varied needs of individuals with DM, healthcare systems can alleviate the adverse effects of the disease, promote equitable access to high-quality care, and enhance population health outcomes. Moreover, fostering collaborations among healthcare providers, policymakers, community organizations, and stakeholders is crucial for fostering a cooperative and sustainable approach to addressing the escalating burden of DM on a global scale.

3. Pharmacological Therapies for Diabetes Mellitus

Effective pharmacological treatment and long-term control of diabetes mellitus have remained a global health concern for many years. Oral hypoglycaemic agents with or without insulin therapy remain the mainstay of treatment in the majority of patients. These medications from the different classes can be used alone or in combination with 2 or more drugs to achieve desired glycaemic control for an individual patient.

A. Oral Antidiabetic Agents

1. Sulfonylureas

Sulfonylureas induce their hypoglycaemic effects by binding to specific sulfonylurea receptors present on pancreatic ß-cells, resulting in insulin secretion. These agents have been broadly used in the treatment of T2DM since the 1950s (Roumie et al., 2012). However, the use of first-generation sulfonylureas was limited by their lower binding affinity and frequent toxicities (Sola et al., 2015). At present, only second-generation agents including glimepiride, glipizide, glibenclamide, and gliclazide are commonly used in practice. They are commonly administered

15-30 minutes before meals (Aquilante, 2010). The frequently encountered side effect of these agents is hypoglycemia, which can be severe and rarely fatal in some patients. Elderly patients and those with liver and kidney diseases are prone to developing hypoglycemia, as these drugs are metabolized by the liver and excreted in the urine (Yousef et al., 2018).

2. Biguanides

At present, Metformin is the only agent used in the clinical practice from this class. It works by enhancing insulin sensitivity of the liver and decreasing glucose production from the liver. It does not have any impact on the insulin release (Lin et al., 2018). Hence, incidences of hypoglycemia in diabetic as well as non-diabetic patients are rare. Additionally, this agent exerts a beneficial effect on lipid profile, promotes weight loss, and potentially prevents macro and micro-vascular complications of T2DM (Foretz et al., 2014). Owing to its numerous benefits and favorable toxicity profile, metformin is recommended as the first-line treatment in patients with T2DM, with a starting daily dose of 500 mg after meals. Generally, metformin is not associated with any serious side effects, however, the incidences of GI tolerance at higher doses limit its usage in some patient (Rena et al., 2017).

3. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

The currently approved DPP-4 inhibitors include vildagliptin, sitagliptin, saxagliptin, teneligliptin, linagliptin, and gemigliptin. These agents exert their hypoglycaemic effects by inhibiting the enzyme dipeptidyl peptidase-4, which is responsible for proteolytic cleavage of incretin hormones including glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1) (Brunton, 2014). These hormones are released from the intestine following a meal. Higher levels of these hormones in the blood result in the stimulation of insulin secretion and inhibition of glucagon release from the pancreas (Padhi et al., 2020). Additionally, GLP-1 inhibits gastric emptying and reduces food intake by central anorexic effects (Pathak et al., 2010). In routine clinical practice, these agents are used in combination with metformin as the second line of treatment. However, they can also be used as monotherapy or as a therapeutic adjuvant to other oral hypoglycaemic agents, or insulin. These agents should be used with caution in patients with renal insufficiency, as the majority of agents from this class are excreted by the kidney (Singh, 2014). The **Error! Reference source not found.** depicts the Mechanism of GLP-1 receptor agonists and DPP-4 inhibitors.

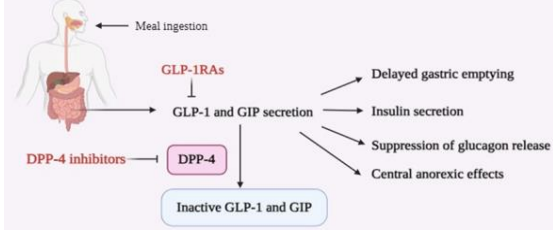

Figure 1: Mechanism of action of GLP-1 receptor agonists and DPP-4 inhibitors, Glucagon-Like Peptide-1 receptor agonists (GLP-1RAs); glucose-dependent insulinotropic peptide (GIP); Dipeptidyl Peptidase-4 (DPP-4)

4. Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors

The majority of filtered glucose gets reabsorbed by the SGLT-2 receptors present in the proximal convoluted tubule. Inhibition of these receptors results in glycosuria, excreting nearly 60-90 grams of glucose through the urine per day (Lupsa & Inzucchi, 2018). SGLT-2 inhibitors have a favourable effect on weight loss and blood pressure. Empagliflozin, dapagliflozin, and canagliflozin are agents available in this class, exhibiting comparable levels of safety and efficacy.(Thomas & Cherney, 2018) The biggest concern related to these agents is their predisposition to causing urinary and genital infections owing to their mechanism. These agents are infrequently used as a monotherapy and rather utilized as an adjunct to other anti-diabetic agents (Tahrani et al., 2016).

5. Thiazolidinediones

These agents are also known as insulin sensitizers, as they activate peroxisome proliferator-activated receptor – γ (PPAR- γ) expressed in insulin-sensitive tissues such as adipose tissue, skeletal muscle, and liver (Eldor et al., 2013). Activation of PPAR- γ stimulates the transcription of insulin-responsive genes, leading to the enhancement of GLUT4 expression, which is a glucose transporter responsible for glucose uptake (Yki-Järvinen, 2004). Hence, glucose and lipid metabolism are positively altered by these mechanisms, which also account for the beneficial effects of these drugs on a patient's lipid profile (Rizos et al., 2016). Pioglitazone and rosiglitazone are two agents from this class. These agents are commonly used along with other oral hypoglycaemic agents, but not insulin (Jearath et al., 2016). Several reports have suggested that combining these drugs with insulin may result in fluid retention, weight gain, and precipitation of heart failure. The peak therapeutic benefit of these agents is commonly observed following 8-12 weeks of therapy (Davidson et al., 2018).

6. Meglitinides

Meglitinides, also known as non-sulfonylurea insulin secretagogues, include nateglinide and repaglinide. The most distinctive feature of these agents is their rapid onset and short-lived duration of action, making them particularly useful in decreasing post-prandial glucose levels. Therefore, these agents are administered 1-30 minutes before meals (R. Guardado-Mendoza et al., 2013). These agents exert their rapid hypoglycaemic effects by binding to the non-sulfonylurea receptors present on pancreatic ß-cells and consequently enhancing insulin secretion (Obale & Banerjee, 2017). However, the resulting insulin secretion from these agents depends on the presence of glucose. As the glucose levels start falling within the blood, insulin secretion decreases as well. Hence, these drugs have lower incidents of hypoglycemia compared to sulfonylureas (Rodolfo Guardado-Mendoza et al., 2013).

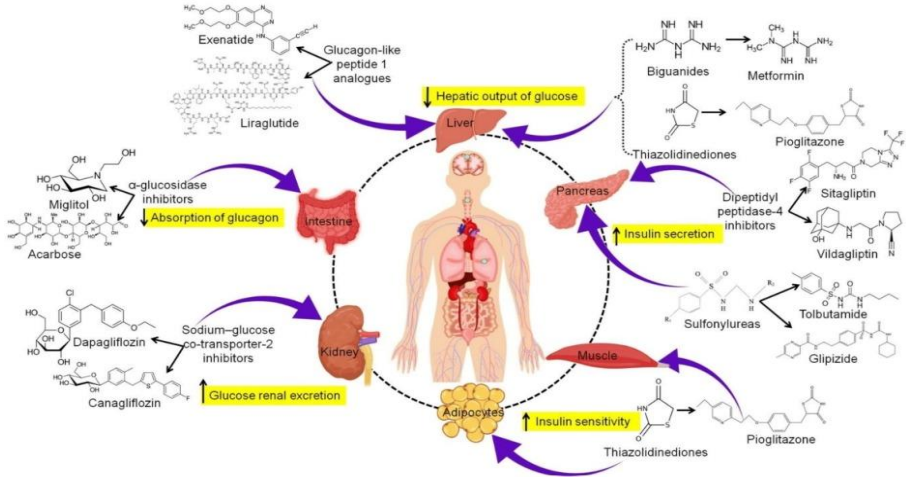

Figure 2: Different anti-diabetic agents and their mechanism of action Adapted from (Vijay Mishra et al., 2021).

B. Injectable Antidiabetic Agents

1. Insulin Therapy

In patients with diabetes mellitus, insulin plays a vital role in achieving glycaemic control by mimicking the physiological pattern of insulin secretion. It is the mainstay of therapy in patients with type-1 diabetes mellitus. In T2DM, it is used when a patient does not optimally respond to oral hypoglycaemic agents alone or in combination. Oftentimes, many patients and physicians are hesitant to start insulin therapy owing to weight gain, hypoglycemia, and fear of taking painful injections every day. Hence this therapeutic option is exercised majorly when lifestyle modification and two or more hypoglycaemic agents are found to be ineffective or non-tolerated (Swinnen et al., 2009). However, a study by Weng et al. highlighted that in patients with newly diagnosed T2DM, a short course of insulin therapy was beneficial for maintaining ß-cell function, causing improved and prolonged glycaemic control. Whenever necessary, insulin therapy should always be tailored according to individual patient needs. While designing the regimen, cost-effectiveness, blood and urine glucose levels, and HbA1c levels, along with the patient's comorbidities and the presence of macro or micro-vascular complications should be considered (Pettis et al., 2019).

a. Types of insulin

Different types of insulin preparations can be classified based on their source and modifications present in the original insulin chain. They are broadly divided into human insulin and analogue insulin. (Swinnen et al., 2009). Human insulin is derived using recombinant DNA technology, designed to closely resemble the insulin produced by the human body. It includes regular and Neutral Protamine Hagedorn (NPH) insulin. Regular insulin contains unmodified insulin with a small amount of zinc for stability. It is commonly used to decrease post-prandial rise in blood

glucose levels. (Jacob et al., 2018). It is commonly administered 30-60 minutes before meals. NPH insulin is an intermediate-acting insulin that contains protamine to complex insulin molecules. It has the onset of action of 1-2 hours, commonly used to provide glycaemic control between meals (Donner & Sarkar, 2015).

b. Insulin analogs

They are chemically modified versions of human insulin, produced using recombinant DNA technology. They have identical pharmacodynamic effects to human insulin but differ in pharmacokinetic aspects. It improves several characteristics of human insulin including peak, onset, and duration of action (Jacob et al., 2018). Insulin analogues can be divided into three categories based on their duration of action.

I. Rapid-acting: Insulin Lispro, insulin Aspart, and insulin Glulisine are examples of rapid-acting insulin analogues. These formulations need to be administered 15-20 minutes before meals. This shorter duration of pre-meal injection is more manageable for patients, which results in greater adherence to the treatment (Leohr et al., 2020).

II. Long-acting: Insulin degludec, insulin Glargine, and insulin Detemir are types of long-acting insulin analogs. In insulin-deficient patients, these agents inhibitors hepatic gluconeogenesis to prevent the rise in glucose levels during the fasting state. When injected into the subcutaneous tissue, these formulations are designed to precipitate at the physiological pH. This creates a depot from which the insulin is released in small amounts throughout the day. It is suitable for once-in-a-day injections to provide continuous insulin action. It is not suitable to control post-prandial glucose peaks, for which rapidly acting formulations should be used (Home & Ashwell, 2002).

2. Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

GLP-1 receptor agonists have recently been introduced in the armamentarium of hypoglycaemic agents. These drugs mimic the actions of the endogenous GLP-1 receptor, which is responsible for the secretion of insulin in response to an increase in glucose levels (Nauck & Meier, 2019). Additionally, these agents are responsible for suppressing glucagon release, delaying gastric emptying, and inducing the feeling of satiety, leading to weight loss as well (Reed et al., 2020). Additionally, these agents suppress hepatic glucose production leading to improved glycaemic control. They are administered by subcutaneous injection and consist of semaglutide, exenatide, liraglutide, dulaglutide, and lixisenatide. The extent of blood glucose reduction by these agents is influenced by baseline glucose levels in individual patients (Berra et al., 2020). A study by Berra et al. reported that patients with high HbA1c levels exhibited greater glycemic control following dulaglutide administration for 6 months (Berra et al., 2020). The most prominent side effects related to GLP-1 agonists are GI problems, pancreatitis, and nodule formation caused by the injection (Bunck et al., 2011).

C. Novel Pharmacotherapies and Emerging Treatments

Recent technological advancements have unveiled a new era of diabetes treatment. Nanotechnology has emerged as a transformative field with profound implications in various drug delivery systems. Owing to the high surface-to-volume ratio of nanocarriers, the same drug

concentrations can yield better bioavailability and receptor binding (Rai et al., 2016). Researchers are optimistically exploring nanocarriers as a promising approach to the treatment of diabetes mellitus. Polymer-based nanoparticles, liposomes, and inorganic nanoparticles are the most commonly utilized nanotechnology-based drug delivery systems in T2DM (Zhao et al., 2020). These nanocarriers improve the stability of drugs and protect them against enzymatic degradation (V. Mishra et al., 2021). Additionally, they deliver drugs to only desired areas and control the release of drug molecules over a long period. This results in improved therapeutic impact and a reduction in adverse effects (Naser et al., 2021).

Insulin pumps are gaining popularity as a superior therapy alternative due to their practicality and ease of use (Peters et al., 2017). They are designed to imitate physiological insulin release by continuous delivery of small amounts of insulin adapted to individual circadian rhythms. With ongoing technological advancements, these agents are becoming smaller and more user-friendly. They offer precise dosing, flexibility, and reduced injection frequency, significantly altering patients' quality of life (Nawaz et al., 2017). Another novel treatment modality such as tissue engineering is under development, which is aimed at restoring or improving pancreatic tissue function (Svendsen & Holst, 2021). Tissue engineering fixes the damaged tissue by using stem cells, scaffolds, and growth factors (Harrison & Surgery, 2015). Further investigations into these approaches hold promise for the advancements of diabetes treatments in the future. Moreover, intensive research on cell therapy and gene therapy in the treatment of T2DM is currently underway (Lin & Anseth, 2011).

4. Clinical Guidelines for the Management of Diabetes Mellitus

In this regard, the management recommendations for diabetes are important, strengthening the quality of care for patients with diabetes. These are a guideline in a setting of evidence-based practice, bringing together the most recent results from clinical trials and new advances in technology. Periodic revisions to these recommendations ensure they retain current-state results in the field and enable all healthcare professionals to have up-to-date information to facilitate optimum care on consensus-driven recommendations. They facilitate clinical decision-making, and outcomes such as quality of care are improved while health practices are in line with the newest evidence and best practices in the care of diabetes (Yu et al., 2022).

A. American Diabetes Association (ADA) Guidelines

The American Diabetes Association guidelines are a comprehensive set of recommendations for managing diabetes—one that attempts to optimize patient care and outcomes covering all aspects, including prevention, diagnosis, treatment, and ongoing management (ElSayed et al., 2023). It guides lifestyle interventions, such as diet and exercise, in addition to pharmacological therapies, including insulin and oral medications. The key focus of the ADA guidelines concerns personalized care, as individual circumstances for each patient are very different. The ADA guidelines outline personalized treatment that will be tailor-made according to such factors as age, comorbidities, and preferences of the patient (F. Sugandh et al., 2023). The guidelines also recognize the importance of patient education and self-management in the achievement of

optimal results. The ADA guidelines also recognize technology in the management of diabetes, including continuous glucose monitoring systems, and insulin pumps. It makes recommendations on how to integrate these technologies into patient care to improve glycemic control and reduce the risk of complications. Other than that, ADA guidelines also focus on a multidisciplinary approach to diabetes care. This involves healthcare professionals from different disciplines, such as endocrinologists, primary care physicians, dietitians, and diabetes educators, who together ensure comprehensive care and support for patients with diabetes (Agarwal et al., 2022).

Latest guidelines have emphasized personalized care for diabetes prevention, screening, intervention, and management and the inclusion of new technologies in the process of prevention, along with concentrating patient-oriented targets in type 2 diabetes prevention. ("Summary of Revisions: Standards of Medical Care in Diabetes-2022," 2022). In detail, adults with overweight or obesity who are at substantial risk of developing type 2 diabetes should be referred to comprehensive lifestyle and behaviour modification programs ("Prevention or Delay of Type 2 Diabetes and Associated Comorbidities: Standards of Medical Care in Diabetes-2022," 2022). Furthermore, personalized programs for weight management and comorbidity prevention should be emphasized to prevent diabetes. In addition, the recommendations have emphasized a need for assessment of individual preference regarding technological support in diabetes management ("Diabetes Technology: Standards of Medical Care in Diabetes-2022," 2022). Also, Recent recommendations advocate for initiating screening for prediabetes and diabetes at age 35 ("Prevention or Delay of Type 2 Diabetes and Associated Comorbidities: Standards of Medical Care in Diabetes-2022," 2022), a departure from the previous guideline which suggested starting at age 45. This shift is supported by evidence indicating that widespread screening among individuals aged 35 and older could substantially decrease the national prevalence of undiagnosed prediabetes or diabetes at a reasonable cost. Additionally, the guideline now places greater emphasis on incorporating Time in Range (TIR) alongside A1C in glycemic assessment ("Diabetes Technology: Standards of Medical Care in Diabetes-2022," 2022). Utilizing a 14-day CGM assessment of TIR and implementing a glucose management indicator can effectively substitute for A1C in clinical management, offering a comprehensive approach to monitoring glucose levels and enhancing patient care.

While the earliest use of metformin in the treatment of diabetes is the same, the latest consensus guideline sets great emphasis on individualized treatment according to the need of the patient. In addition, a considerable stress is given to the early use of SGLT2 inhibitors and GLP-1 receptor agonists, especially in patients with CVD and/or CKD ("Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022," 2022). Furthermore, the updated guidelines prioritize patient-centred treatment objectives rather than a sequential approach to treatment intensification (Matthews et al., 2019). Concerning insulin therapy, the recommendation for combination therapy with GLP-1 receptor agonists persists, with a heightened emphasis on initiating combination therapy at an earlier stage in the treatment regimen (Aroda et al., 2019).

Within the domain of diabetes care, a broader approach toward prevention of complications is advisable. The approaches include controlling glycemia, blood pressure, and lipids, as well as

treatments with cardiovascular and/or kidney disease benefits ("Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022," 2022). Specifically, individuals with type 2 diabetes and atherosclerotic cardiovascular disease (ASCVD) are encouraged to consider SGLT2 inhibitors and/or GLP-1 receptor agonists (Zinman et al., 2015). Moreover, for those with type 2 diabetes and established heart failure with reduced ejection fraction, the recommendation leans towards SGLT2 inhibitors, given their proven efficacy in reducing heart failure and cardiovascular mortality (Packer et al., 2020).

The highlight of the newer guidelines is the active use of CGM devices. Unlike earlier guidelines that recommended CGM mainly for users of multiple daily injections or continuous subcutaneous insulin infusion, the current recommendation now takes in users of long-acting insulin from the early stages of insulin-dependent diabetes diagnosis (Martens et al., 2021). Furthermore, CGM device usage is advocated for children with diabetes using insulin, with the additional endorsement of Automated Insulin Delivery (AID) systems for children with type 1 diabetes. This expansion underscores the significance of diabetes management within educational settings, as highlighted in the guidelines ("Children and Adolescents: Standards of Medical Care in Diabetes-2022," 2022). Additionally, due to the COVID-19 pandemic, CGM devices have seen increased adoption to reduce healthcare provider-patient contact, which is anticipated to propel the integration of technology into diabetes management practices ("Diabetes Care in the Hospital: Standards of Medical Care in Diabetes-2022," 2022; Aljehani et al., 2020; Pasquel & Umpierrez, 2020; Wallia et al., 2020) and it is shown in Table 1.

Table 1: A summary of general recommendations of ADA guidelines.

Aspects	Summary of ADA guidelines
Overview	ADA guidelines emphasize personalized diabetes care, integrating lifestyle interventions, pharmacological therapies, and technology (ElSayed et al., 2023).
Recent revisions	Focus on individualized care, intensive lifestyle interventions for high-risk individuals, and early screening for prediabetes/diabetes (Committee, 2021).
Technological Integration	Encourages CGM and insulin pump use, emphasizes Time in Range (TIR) monitoring, and individual preference-based technology adoption.
Medication Updates	Advocates earlier use of SGLT2 inhibitors and GLP-1 receptor agonists, personalized treatment plans, and combination therapy with insulin (Zinman et al., 2015).
Complication management	Holistic approach to mitigate complications, prioritizing cardiovascular and kidney disease benefits, especially in high-risk populations.
CGM device utilization	Recommends CGM for all insulin-dependent patients, including children, and highlights increased adoption during the COVID-19 pandemic for remote monitoring (Martens et al., 2021).

B. European Association for the Study of Diabetes (EASD) Guidelines

The European Association for the Study of Diabetes (EASD) Guidelines represent a cornerstone in the management of diabetes, providing comprehensive recommendations for healthcare professionals to optimize patient care. These guidelines, crafted through a rigorous process involving experts in the field, offer evidence-based insights tailored to the dynamic landscape of diabetes management (Inzucchi et al., 2012). At its core, the EASD Guidelines emphasize a patient-centred approach, recognizing the heterogeneity of diabetes and the importance of individualized care. By considering factors such as age, comorbidities, and patient preferences, healthcare providers can tailor treatment strategies to maximize efficacy and minimize risks (Davies et al., 2022). One of the key principles underscored by the EASD Guidelines is the

importance of early detection and intervention. Timely diagnosis allows for prompt initiation of appropriate therapies, which can significantly impact disease progression and outcomes. Moreover, the guidelines advocate for regular monitoring and assessment to track disease progression and treatment response, enabling timely adjustments as needed (Herman et al., 2015). In alignment with the principles of evidence-based medicine, the EASD Guidelines prioritize interventions with proven efficacy and safety profiles. This includes lifestyle modifications, such as diet and exercise, which play a fundamental role in the management of diabetes (Bagnasco et al., 2014). Additionally, the guidelines provide clear recommendations regarding pharmacological interventions, taking into account factors such as drug efficacy, safety, and patient preferences ("Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020," 2020).

The consensus report from the ADA and EASD in 2018, with an update in 2019, emphasized the importance of considering key clinical factors in selecting treatments for lowering blood glucose. In individuals with established CVD or those at significant risk, therapies using GLP-1 RA were recommended over SGLT2 inhibitors (SGLT2i). However, for patients with heart failure (HF), especially those with reduced ejection fraction, or chronic kidney disease (CKD), SGLT2 inhibitors were recommended due to their positive effects on heart hospitalization and CKD progression (Rolek et al., 2023). Since the 2019 update, there have been numerous trials and updated meta-analyses concerning cardiovascular, renal, and HF outcomes, especially regarding SGLT2i. These new studies evaluated different patient subgroups based on various criteria such as existing CVD, metformin use, CKD stage, previous HF, and age. This fresh evidence has been meticulously gathered and assessed to update the clinical practice guidelines (Davies et al., 2022).

The guidelines underscore the concept that Type 2 diabetes mirrors an accelerated biological aging process. Consequently, individuals with Type 2 diabetes experience declines in physical capabilities, primarily due to skeletal muscle dysfunction. Research indicates that middle-aged individuals with Type 2 diabetes exhibit functional exercise capacities similar to those a decade older in the general population. This disparity places individuals with Type 2 diabetes at heightened risk of impaired physical function and frailty, ultimately diminishing their quality of life and increasing healthcare utilization. Consequently, frailty is gaining recognition as a significant complication of Type 2 diabetes and warrants attention as a crucial target for intervention (Rolek et al., 2023).

The EASD guidelines highlight the challenge of making informed treatment decisions for older adults (aged >65 years) with diabetes due to their limited representation in clinical trials. Studies such as the ADVANCE trial have shed light on the association between frailty and poorer outcomes, suggesting that more frail individuals may benefit less from intensive control of blood glucose and blood pressure levels (Nguyen et al., 2021). However, recent improvements in our ability to select medications stem from regulatory mandates requiring the inclusion of older participants in trials evaluating the efficacy and safety of new diabetes drugs. The rise in rates of impaired glucose tolerance, impaired fasting glucose, and type 2 diabetes among adolescents and young adults parallels the increasing prevalence of obesity. In the USA, approximately one in five adolescents and one in four young adults now experience impaired glucose metabolism,

elevating their risks of progressing to type 2 diabetes, CKD, and CVS complications (Andes et al., 2020). Minority populations, including Hispanic, non-Hispanic Black, Asian/Pacific Islander, and American Indian communities, are disproportionately affected, with over half of new type 2 diabetes diagnoses occurring within these groups during childhood and adolescence (Dabelea et al., 2007). Affected young individuals exhibit faster deterioration in blood glucose levels, reduced response to diabetes medication, and accelerated development of diabetes-related complications ("Impact of insulin and metformin versus metformin alone on β-cell function in youth with impaired glucose tolerance or recently diagnosed type 2 diabetes %J Diabetes Care," 2018). The onset of disease at an early age, coupled with elevated hyperglycemia levels and the presence of numerous cardiometabolic risk factors, collectively heighten the likelihood of adverse outcomes among adolescents and young adults with impaired glucose tolerance, impaired fasting glucose, and diabetes. Furthermore, the majority of children and adolescents diagnosed with type 2 diabetes will experience microvascular complications by the time they reach young adulthood (Bjornstad et al., 2021). It is crucial to recognize that younger individuals diagnosed with type 2 diabetes face a significantly elevated risk of complications and should be managed accordingly. Considering early initiation of combination therapy may be prudent, given findings from the VERIFY trial indicating that this approach yields better and longer-lasting improvements in blood glucose levels compared to using metformin alone, particularly for individuals with both early-onset (under 40 years of age) and later-onset diabetes (Chan et al., 2021).

In summary, the EASD guidelines provide several consensus recommendations for managing type 2 diabetes effectively. Firstly, they emphasize the importance of offering ongoing diabetes self-management education and support programs to all individuals with the condition. Additionally, healthcare providers and systems are urged to prioritize person-centered care. When selecting glucose-lowering medications, optimizing medication adherence should be a specific consideration. Medical nutrition therapy is recommended, focusing on identifying healthy dietary habits that are both feasible and sustainable to help individuals achieve their metabolic and weight goals. Physical activity is highlighted as a crucial component of type 2 diabetes management, with recommendations for both aerobic and resistance training. Metabolic surgery may be considered for individuals with a high BMI who do not respond well to non-surgical treatments. GLP-1 receptor agonists or SGLT2 inhibitors are suggested for individuals with established cardiovascular or kidney disease, with SGLT2 inhibitors specifically recommended for those with heart failure. GLP-1 receptor agonists or SGLT2 inhibitors may also be considered for individuals with multiple cardiovascular risk factors. Importantly, the decision to use these medications should be independent of metformin use. Finally, in younger individuals with diabetes, early combination therapy may be considered, and women of reproductive potential should receive counselling regarding contraception and medication safety (Davies et al.).

C. International Diabetes Federation (IDF) Recommendations

The IDF recommends comprehensive diabetes management, advocating for patient education and tailored care. Emphasizing lifestyle modifications, they stress regular physical activity and a balanced diet. Medication adherence and personalized treatment plans are essential. For

individuals with diabetes complications or high cardiovascular risk, prioritizing cardiovascular health is crucial. Additionally, the IDF highlights the importance of psychosocial support and mental health management. They underscore the need for collaborative efforts among healthcare providers, policymakers, and communities to address the growing global burden of diabetes effectively (Sun et al., 2022).

According to the IDF, around 537 million people, which is about 10.5% of the global adult population, were living with diabetes in 2021. They predict that by 2045, this number will rise to about 783 million, affecting approximately 12.2% of adults worldwide. Additionally, about 541 million individuals, or 10.6% of adults globally, had impaired glucose tolerance (IGT) in 2021, putting them at higher risk of developing type 2 diabetes (T2D). The IDF expects this number to increase to around 730 million, or 11.4% of adults, by 2045. These statistics underscore the urgent need for awareness and effective diabetes prevention strategies worldwide (Sun et al., 2022). Individuals with T2D face higher chances of experiencing complications affecting both small and large blood vessels, as well as conditions like obstructive sleep apnea (OSA), cystic fibrosis-related diabetes mellitus (CFRD), metabolic dysfunction-associated steatotic liver disease (MASLD), and premature death. Recently, there's been discussion, including a published petition, about using the 1-hour plasma glucose (1-h PG) as a potential replacement for current diagnostic criteria, with several review articles exploring this topic (Jagannathan et al., 2018) (Fiorentino et al., 2018) (Bergman et al., 2020) (Jagannathan et al., 2020) (Bergman et al., 2017). This suggests ongoing efforts to improve diagnostic methods and care for those with T2D. The IDF Position Statement highlights the significance of using 1-hour post-load plasma glucose (1-h PG) levels to predict progression to type 2 diabetes (T2D) and related complications. A 1-h PG of ≥155 mg/dL (8.6 mmol/L) during an OGTT indicates increased risk, while a level of ≥209 mg/dL (11.6 mmol/L) confirms T2D. Early detection with 1-h PG thresholds allows for timely intervention, potentially averting T2D development. Healthcare systems should consider integrating 1-h PG screening, followed by lifestyle interventions for those with elevated levels, and confirmatory testing for T2D diagnosis. This approach offers a promising strategy for combating the global diabetes epidemic (Bergman et al., 2024) and displayed in Figure 3.

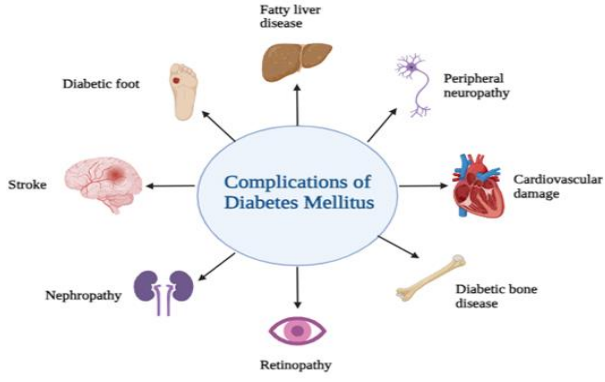

Figure 3: Macro- and Micro-vascular complications associated with Type-2 Diabetes Mellitus.

5. Advances in Diabetes Technology

Advances in diabetes technology refer to the rapid evolution of tools and devices designed to enhance the management and monitoring of diabetes. These innovations encompass a wide range of technological solutions aimed at improving glucose control, reducing complications, and improving quality of life for individuals with diabetes (Ashrafzadeh & Hamdy, 2019). From continuous glucose monitoring (CGM) systems that provide real-time glucose readings to insulin pumps that deliver precise insulin doses, these advancements offer unprecedented levels of convenience, accuracy, and customization in diabetes care (Yoo & Kim, 2023). Furthermore, the integration of artificial intelligence and data analytics has enabled personalized insights and predictive capabilities, empowering patients and healthcare providers to make more informed decisions (Johnson et al., 2021) . The ongoing progress in diabetes technology holds promise for revolutionizing the way diabetes is managed, ultimately leading to better outcomes and improved overall well-being for those living with the condition.

A. Continuous Glucose Monitoring (CGM) Systems

CGMs have been around since 1999, and they give both patients and doctors a better picture of how blood sugar levels change throughout the day by checking glucose levels every 5–15 minutes. With CGMs, people can see trends, patterns, and how much time they spend within or outside their target blood sugar range. This helps them adjust their insulin doses more accurately to avoid high or low blood sugar levels. Using CGMs regularly can lead to better control of blood sugar levels, less time spent with high or low blood sugar, and ideally, a lower risk of complications from type 1 diabetes. Studies have found that CGMs are most effective for people who start with higher HbA1c levels (a measure of average blood sugar over time) and for those who use the sensors frequently (Danne et al., 2017) (Phillip et al., 2012). For example, one analysis from 2011 showed that using a CGM led to an average decrease of 0.3% in HbA1c compared to traditional self-monitoring of blood glucose (SMBG). Additionally, if every extra day someone uses a CGM, their HbA1c may drop by 0.15% (Pickup et al., 2011). CGMs work by inserting a small sensor under the skin to measure glucose levels in the fluid between cells. This data is then sent to a device that displays the information (Olczuk & Priefer, 2018). The accuracy of CGMs is often assessed by comparing their readings to those from a blood glucose meter. Modern CGMs typically have an accuracy level of less than 10%, as measured by the mean absolute relative difference (MARD) (Gifford, 2013).

CGM can offer real-time and retrospective data to identify hypoglycemic and hyperglycemic excursions, anticipate the onset of hypoglycemia, and measure the wide range of glucose variations, or glycemic variability (Dave et al., 2021). All CGM devices certified by the FDA come with 24-hour telephone support. By using a CGM, patients and their healthcare provider can fine-tune their prescription therapy and gain information on how to improve their behaviour to achieve glycemic control (Cappon et al., 2019). Furthermore, the present research is gradually moving closer to a completely working artificial pancreas by connecting CGM measurement with automatically controlled insulin delivery (Nihaal Reddy, 2023). Professional CGM involves using equipment owned by healthcare providers to gather data on glucose levels. Unlike personal CGMs that show real-time results, professional CGM devices collect readings over time and are

then downloaded for analysis, similar to how 24-hour cardiac monitor tracks heart rhythms after the fact. This method helps healthcare providers get an unbiased view of a person's glucose patterns in their everyday lives. According to recommendations from the Endocrine Society, professional CGM can be helpful for adults with diabetes in several ways. It can detect nighttime low blood sugar (hypoglycemia), the rise in blood sugar in the early morning (dawn phenomenon), and high blood sugar after meals (postprandial hyperglycemia), and can assist in deciding the best treatments for managing diabetes (Peters et al., 2016). Different types of CGM devices are available, some of them are discussed below:

Medtronic

In 1999, Medtronic, based in Dublin, Ireland, introduced the Sof-sensor, marking the debut of CGM technology. Although it was a breakthrough for at-home glucose monitoring, users experienced discomfort during insertion and while wearing the device. Additionally, its accuracy fell short, with a MARD of 19.7%. In 2011, Medtronic launched the Enlite sensor as an improvement (Gifford, 2013). This CGM addressed the discomfort and accuracy issues and introduced predictive alerts. These alerts notify users in advance of potential high or low blood sugar events, offering added peace of mind and control over their diabetes management (Bailey et al., 2014). The integrated Medtronic Paradigm, 530G, and 630G insulin pumps can access the CGM data. The CGM connects wirelessly to the Contour Next Link glucometer from Ascensia Diabetes Care (Basel, Switzerland), and a finger-stick calibration is needed every 12 hours. Data management solutions like Glooko, Tidepool, Diasend, or Carelink can receive the CGM data and process it (Bailey et al., 2014).

In 2017, Medtronic introduced the Guardian 3 CGM, which integrates with the Medtronic 670G insulin pump as part of an innovative hybrid closed-loop system for monitoring glucose and administering insulin. To ensure precise readings, users must calibrate the device twice daily. These regular calibrations yield a MARD ranging from 9.1% to 10.6%, depending on the placement of the sensor. More frequent calibrations, about three to four times daily, can enhance the device's accuracy, reducing the MARD to between 8.7% and 9.6% (Christiansen et al., 2017).

Dexcom:

Dexcom began working on its own CGM technology, culminating in the launch of the Dexcom STS CGM system in 2006, followed by the Dexcom SEVEN® CGM in 2009. The Dexcom SEVEN® offered a MARD of 16.5% and could be used continuously for up to a week. In 2012, Dexcom made further advances with the introduction of the Dexcom G4®, which boasted a reduced MARD of 12.6%, marking a significant improvement in accuracy (Gifford, 2013). In 2015, Dexcom unveiled the Dexcom G5® Mobile system, which received approval for use in patients aged two years and older (Rodbard, 2016). This CGM system marked a significant milestone as the first of its kind to be approved for non-adjunctive use, meaning that it could be relied upon for making insulin dosing decisions without the need for confirmation from finger-stick tests. Despite requiring occasional finger-stick calibrations, the G5 boasted a MARD of 9%, ensuring precise and reliable glucose monitoring (Cappon et al., 2017).

In March 2018, the Dexcom G6® received approval from the FDA, marking a significant advancement in continuous glucose monitoring technology. Unlike its predecessors, the G6 is

factory-calibrated, eliminating the need for finger-stick calibrations. Despite this change, it maintains a MARD of 9%, ensuring accurate glucose readings (Shah et al., 2018). The G6 offers the flexibility to operate as a standalone CGM or to seamlessly integrate with compatible insulin pumps, paving the way for future innovations in diabetes management. Additionally, users can now wear the sensor for up to 10 days, and unlike earlier versions, it is unaffected by acetaminophen, providing greater convenience and reliability (Bailey et al., 2018).

Freestyle Libre:

In 2016, Abbott's FreeStyle Libre entered the market as a game-changer in continuous glucose monitoring. This CGM is not only water-resistant but also disposable, offering hassle-free monitoring without the need for calibration. MARD of 10%, users can trust the accuracy of their glucose readings (Rodbard, 2016). Originally approved for 10 days of use, the Libre's lifespan has been extended to 14 days, accompanied by a quicker one-hour warm-up period. Available for individuals aged 18 and older in the US and 4 and older in Europe, the FreeStyle Libre provides convenient and reliable glucose monitoring for a wide range of users (Food, 2018). The FDA approved the FreeStyle Libre 3 CGM system in June 2022 for use in diabetics who are at least 4 years old. It is a real-time system that continually scans and shows glycemic data without requiring users to scan the sensor with a reader or smartphone to see results, in contrast to earlier intermittently scanned FreeStyle Libre systems ("ABBOTT'S FREESTYLE LIBRE® 3 RECEIVES U.S. FDA CLEARANCE - FEATURES WORLD'S SMALLEST, THINNEST AND MOST ACCURATE 14-DAY GLUCOSE SENSOR," 2022).

Senseonics:

Senseonics offers the Eversense® CGM, an implantable device approved in 2018 for up to 90 days of use in the US (180 days in Europe). Unlike traditional CGMs, the Eversense sensor is inserted under the skin during a medical procedure, typically done at quarterly appointments. This process involves local anaesthesia and a small incision, which may cause some patients to feel anxious. The device requires calibrations every 12 hours and boasts a MARD of 8.8%, ensuring accurate glucose monitoring (Bailey et al., 2018). The Ever Sense E3 CGM system received FDA approval in February 2022. Adults with diabetes who are at least 18 years old are eligible to utilize this implantable continuous glucose monitoring sensor for a maximum of six months. For the first twenty-one days of its six-month operation, this system needs to be calibrated twice a day; thereafter, it needs to be done once a day. It is the only CGM featuring wearable transmitter-based on-body vibration alerts and a 24-hour warm-up period (Garg et al., 2022).

Table 2: Different types of CGM devices along with their important features.

Uses	Device	Launch year	Duration of Use	MARD	Noble Features
Continuous Glucose Monitor (CGM)	Sof-sensor	1999	3 days	19.7 %	Initial discomfort and accuracy issues; predictive alerts
	Enlite	2011	6 days	9.1%-10/6%	Improved accuracy and comfort; predictive alerts
	Guardian 3	2017	7 days	8.7%-9.6%	Integration with insulin pumps; hybrid closed-loop system
	SEVEN®	2009	7 days	Unknown	Moderate accuracy; continuous use
	G4®	2012	7 days	12.6%	Improved accuracy

	G5® Mobile	2015	7 days	9%	FDA-approved for non-adjunctive use; no confirmation from finger-stick tests
	G6®	2018	10 days	9%	Factory-calibrated; no finger-stick calibrations required; unaffected by acetaminophen
	FreeStyle Libre	2016	10 days	10%	Water-resistant; disposable; no calibration required
	FreeStyle Libre 3	2022	14 days	Unknown	Real-time system; no scanning required; extended lifespan
	Eversense®	2018	90 days	8.8%	Implantable; local anaesthesia required; calibrations every 12 hours
	Eversense E3	2022	6 months	Unknown	Wearable transmitter-based vibration alerts; 24-hour warm-up period

B. Insulin Delivery Systems

Insulin delivery systems are crucial for managing diabetes by ensuring that insulin, a vital hormone that regulates blood sugar, is administered effectively. These systems vary in complexity and function to cater to the diverse needs and lifestyles of individuals with diabetes. There are several types of Insulin delivery systems, Insulin syringes, Insulin pens, Insulin pumps, Inhaled insulin, Implantable pumps, and Insulin jet injectors (Shah et al., 2016).

Insulin Injections:

Eli Lilly and Novo Nordisk have developed advanced insulin pens that feature memory capabilities. These pens record the time, date, and amount of insulin administered, allowing for accurate tracking of past doses. Accessories like the Timesulin® cap, introduced in 2011, enhance regular insulin pens by displaying the time since the last injection. More recently, the Gocap has been introduced, which fits most insulin pens and pairs with a smartphone app via Bluetooth. This app not only tracks insulin doses but also records dietary and exercise data, and sends reminders for doses that are missed or deviate from the norm. It facilitates data sharing with family and medical professionals, helping to optimize diabetes management (Zimmerman et al., 2019). Another smart pen technology is the InPen, which connects to a smartphone app to deliver bolus advice and insulin on-board calculations. The pen is reusable and uses insulin cartridges. Blood glucose averages and trends are also provided by the Dexcom CGM's connection to the InPen app (Bailey et al., 2018). In 2022, A newly made Tempo-linked insulin pen cap and app was approved by the FDA. These items are compatible with the basal and bolus insulin pens made by Eli Lilly. A reusable medical gadget called the Tempo Smart Button is attached to the top of Tempo pens, which are disposable insulin pens that are prefilled by Eli Lilly ("Eli Lilly to start rollout of Tempo personalized diabetes management platform," 2022).

Inhaled Insulin:

Afrezza® is a unique inhaled insulin consisting of Technosphere insulin powder (TI) and gained FDA approval in 2014. It stands as the sole inhaled insulin product on the market (Bailey et al., 2018). When inhaled, Afrezza's TI particles dissolve in the alveoli, leading to rapid systemic absorption of insulin. Compared to subcutaneous insulin, Afrezza reaches its peak effect in just 53 minutes and has a shorter duration of action. Clinical studies have shown Afrezza to result in fewer instances of postprandial hyper- or hypoglycemia. However, its available fixed doses of 4, 8, or 12 units may present dosing challenges for some patients (Klonoff, 2014).

Insulin Pumps:

The initial insulin pump, known as the Biostator, emerged in 1974. Due to its size, it was primarily utilized in hospital settings for managing diabetic ketoacidosis (DKA). (Selam & Charles, 1990) The first commercial insulin pump was introduced by MiniMed (now Medtronic) in the 1980s. Over the past four decades, these devices have undergone significant advancements. Looking forward, the next decade is expected to dramatically change how both patients and doctors interact with insulin pumps and CGMs. Research indicates that insulin pumps enhance control over blood glucose levels, leading to better HbA1c results and fewer instances of hypoglycemia, without an increased risk of DKA, regardless of initial HbA1c levels (Forlenza et al., 2016).

Medtronic:

In 2003, Medtronic introduced innovative technologies, including a wireless insulin pump and glucose meter, followed by the Carelink management software in 2004. The Paradigm Real-Time Revel™ system received FDA approval in 2010, offering both standalone insulin pump functionality and integration with Medtronic's CGM system. This system enabled users to view CGM data directly on the insulin pump screen (Grunberger et al., 2014). The MiniMed 530G system, released in 2013, provided similar features, serving as a standalone insulin pump or integrating with the Enlite CGM for enhanced monitoring capabilities (Mariani et al., 2017).

The MiniMed 630G system was introduced by Medtronic in 2016. The 630G boasts a colour screen along with features that are similar to the earlier insulin pumps, such as basal and bolus increments, insulin cartridge size, and threshold suspension capability (Zimmerman et al., 2019). Medtronic's latest innovation, the 670G system, introduces the first hybrid closed-loop technology, combining the Guardian 3 CGM with SmartGuard technology. This system offers two modes of operation: "manual mode" functions as a sensor-augmented pump with predictive low glucose suspend (PLGS) capability, while "auto mode" adjusts insulin delivery every 5 minutes to maintain a target glucose level of 120 mg/dL. The algorithm incorporates CGM data and a sensitivity factor that is recalculated daily based on previous insulin doses and the target glucose level (de Bock et al., 2018).

The MiniMed 780G AID system, which has been in use in Europe since 2020, was also approved by the FDA in March 2023. Ages 7 and older with type 1 diabetes are eligible to use this HCL system (Akturk et al., 2024). The Meal detecting technology in the 780G system automatically administers correction boluses every five minutes to optimise glucose levels. Patients who need to take 8–250 units of insulin per day can use it. For automatic mode, the system can be coupled with the Guardian 3 and Guardian 4 CGM systems. When utilising the Guardian 4 sensor in automated mode, users reported requiring fewer fingerstick BGM confirmations than with the 770G system. The Guardian 4 sensor does not require any calibrations with fingerstick BGM (Cordero et al., 2023).

Animas:

The Animas OneTouch Ping® insulin pump gained FDA approval in 2008, featuring radio frequency communication with the OneTouch meter. This allowed for seamless transmission of

blood glucose readings from the meter to the pump, enabling remote programming of insulin delivery (Selam, 2010). In 2014, the Animas Vibe® insulin pump received FDA approval for adults, followed by approval for children aged two years and older in 2016 (Barnard et al., 2015). Animas collaborated with the Juvenile Diabetes Research Foundation (JDRF) in 2010 to develop a hybrid closed-loop system, and subsequent data releases in 2014 and 2016 showcased promising outcomes using the Hypoglycemia-Hyperglycemia Minimizer system in conjunction with the Animas OneTouch Ping insulin pump and Dexcom G4 CGM (Finan et al., 2015).

Tandem:

The t:slim insulin pump was created by Tandem Diabetes Care in 2012 with a great deal of end-user feedback. A touch-screen gadget with a rechargeable battery that lasts up to seven days was developed as a result of surveys and focus groups held to ascertain patient priorities. Important details like the amount of insulin left, the amount of insulin on board, the battery life, and easy access to bolus and pump functions are all displayed on the home screen (Schaeffer, 2012). In 2016, the t:slim X2™ insulin pump made its debut, boasting a sleeker design compared to previous models. What sets the X2 apart is its unique ability to update its software from the comfort of home using a personal computer, a feature previously unseen in insulin pumps. The t:slim X2 is approved for use in patients aged six years and older (Zimmerman et al., 2019). The recent FDA approval of the t:slim X2 marks a significant milestone as the first insulin pump to achieve interoperability. This means it can seamlessly integrate with a range of CGMs, blood glucose meters, and software platforms. This enhanced compatibility opens up a world of possibilities for personalized diabetes care and lays the groundwork for future advancements in closed-loop systems (Berget et al., 2020).

Insulet:

Insulet, based in USA, introduced the OmniPod® insulin pump in 2011, followed by a smaller second-generation pod in 2013. The OmniPod is a tubeless insulin pump that can be worn continuously for up to 72 hours. It is controlled by a personal diabetes manager (PDM), which also doubles as a glucose meter (Zimmerman et al., 2019). A study conducted by Layne et al. revealed that individuals using the OmniPod experienced an average HbA1c reduction of 0.6% over three months, irrespective of their previous treatment regimen (Layne et al., 2016).

The FDA approved The Omnipod DASHTM Insulin Management System in June 2018. This system comes with an upgraded touchscreen PDM and a pod that is Bluetooth enabled. With the help of the PDM, data can be accessed remotely on a different smartphone by connecting this system to the Contour Next One glucose metre (Ly et al., 2019). In 2012, a randomised two-arm open crossover study was conducted to compare the patient satisfaction of standard insulin pumps and the original EPod insulin pump. Although patients were generally satisfied with both types of therapy, the subjects did mention the advantages of the OmniPod, such as its automated cannula insertion and continuous insulin infusion without the need to disconnect (Lebenthal et al., 2012).

The Omnipod 5 automated insulin delivery (AID) system, sometimes referred to as a hybrid closed-loop (HCL) insulin delivery system, received FDA approval in January 2022. This system consists of a tubeless pod insulin pump that is Bluetooth-connected to a Dexcom G6 CGM

sensor. It also includes a mobile app with an integrated bolus calculator and a control algorithm that adjusts insulin supply based on real-time glucose levels (Brown et al., 2021).

C. Artificial Pancreas Systems

Artificial pancreas therapy, also termed closed-loop glucose management, emerges as a revolutionary treatment blending an insulin pump and continuous glucose monitoring with an intelligent control algorithm. This sophisticated system delivers insulin in response to glucose levels, forming a single-hormone approach. Moreover, dual-hormone systems can administer glucagon in a similarly responsive manner. Compared to traditional insulin pumps or sensor-augmented pumps, artificial pancreas technology lightens the patient's burden by autonomously adjusting insulin delivery based on real-time sensor data. Numerous artificial pancreas iterations have been developed, undergoing rigorous evaluation for safety and efficacy in various studies, all demonstrating promising outcomes (Kumareswaran et al., 2011). Initial analyses, including a pooled review of limited inpatient trials and a comprehensive overview up to 2014, provided foundational insights (Battelino et al., 2015). Recent meta-analyses have synthesized evidence from outpatient trials, further illuminating the benefits of artificial pancreas systems for individuals with type 1 diabetes (Weisman et al., 2017). A significant regulatory milestone was achieved with the recent approval by the US FDA of the first artificial pancreas system for use in individuals over 14 years old with type 1 diabetes, following robust outpatient safety assessments (Bergenstal et al., 2016).

A systematic review and meta-analysis by Bekiari et al assessed the effectiveness and safety of artificial pancreas treatment in non-pregnant outpatients with type 1 diabetes. The review included 40 studies with data from 1027 participants across 44 comparisons, evaluating both single hormone and dual hormone systems. Results indicated that artificial pancreas use significantly increased the proportion of time spent within the near normoglycemic range (3.9-10.0 mmol/L) both overnight and over a 24-hour period. Furthermore, these systems showed a favorable impact on reducing the proportion of time with sensor glucose levels above 10 mmol/L or below 3.9 mmol/L compared to control treatments. Sensitivity analyses confirmed the robustness of these findings, particularly when considering trials at low risk of bias or conducted under unsupervised, normal living conditions. Subgroup analyses demonstrated consistent results for both single and dual hormone systems. In conclusion, artificial pancreas systems emerge as an effective and safe option for managing type 1 diabetes in outpatient settings. However, limitations in the existing evidence include variations in outcome reporting, small sample sizes, and short follow-up durations in individual trials (Bekiari et al., 2018).

The FDA approved the iLet Bionic Pancreas AID system in May 2023. The user must first enter their weight to access the three glucose target options available in this system: ordinary, lower, and higher (Russell et al., 2023). When bolusing at mealtime, users do not need to enter any carbohydrate amounts. Rather, patients choose a choice for a usual, more than usual, or less than usual bolus. In response to comparable past meal notifications, the system automatically modifies insulin delivery depending on the user's dosage history. There are no pre-programmed manual settings on the iLet system. The system will demand blood glucose reading

to be entered every 4 hours for up to 72 hours if there is no CGM connection to continue automation. If this happens, the system will switch down entirely.

6. Challenges and Opportunities in Diabetes Management

Despite recent numerous advances in diabetes care, it continues to exert high mortality and morbidity rates. A comprehensive approach is urgently needed to cope with these challenges and prevent diabetes in future generations.

A. Adherence to Treatment Regimens

Poor medication adherence in patients with T2DM is associated with suboptimal glycemic control, increased mortality, morbidity, and healthcare costs.(Huang et al., 2021) A study by Zhang et al. reported that nearly 59.8% of patients with T2DM were non-adherent to their treatment.(Zhang et al., 2021) Factors influencing adherence include patient age, as more elderly patients are non-adherent compared to young individuals. Another factor is alcohol consumption, which negatively impacts adherence apart from accelerating disease progression.(Sahoo et al., 2022) Improved patient education and proper counseling regarding the importance of medication adherence might improve the adherence up to some extent in these patients. Improved adherence to anti-diabetic medications significantly improves glycemic control, thereby reducing complications, hospitalizations, and overall healthcare costs, while promoting better prognosis for patients.(Kirkman et al., 2015)

B. Cost and Accessibility of New Therapies

The accessibility and affordability of newer antidiabetic therapies, such as GLP-1 receptor agonists and insulin analogs are critical issues impacting diabetes care in low and middle-income countries (LMICs).(Barber et al., 2024) Despite the higher burden of T2DM in LMICs, health authorities struggle with increasing costs of diabetes-related expenditures. The cost of insulin represents a huge barrier to access not only in LMICs but also in developed countries like the USA. Many patients tend to underdose themselves to stretch their insulin supply in response to financial constraints.(Fralick et al., 2022) This compromises glycaemic control, leading to complications, and further exacerbating the financial burden on the patient. Efforts to improve access to affordable therapies must involve multiple stakeholders, including governments, policymakers, healthcare providers, pharmaceutical companies, and patient advocacy groups.(Taylor, 2020) Price negotiations, bulk purchasing, and generic drug production can help mitigate medication costs and improve accessibility to all patients with T2DM.(Sonmez et al., 2022)1

C. Integration of Multidisciplinary Care Teams

Multidisciplinary healthcare teams incorporate a diverse group of healthcare professionals collaborating to provide comprehensive care to patients. This approach can be particularly beneficial in patients with diabetes due to the complex nature of the disease and the presence of multiple comorbidities in the majority of patients.(Andersen et al., 2023) Patients with multimorbidity often experience higher rates of hospital admissions and increased healthcare

costs, posing a significant burden on patients and the healthcare sector as well. The involvement of a multifaceted management approach is crucial for addressing the unique needs of each individual with diabetes. For instance, a collaboration between diabetologists and cardiologists presents an opportunity to improve glycaemic control and reduce the risk of cardiovascular complications in patients with T2DM (Tan et al., 2020).

A study by Taieb et al. reported that in hospitalized patients with uncontrolled T2DM, a multidisciplinary approach was found to be beneficial in more than 90% of the study population (Taïeb et al., 2022). In an outpatient setting, patients with complex diseases can be managed by an interdisciplinary team that includes cardiologists, nephrologists, endocrinologists, diabetic foot specialists, and ophthalmologists, in addition to the primary care providers (Bain et al., 2019). This collaborative approach ensures comprehensive management of diabetes-related complications, aiming to effectively manage the associated challenges.

7. Future Directions and Research Implications

A. Personalized Medicine in Diabetes Management

Personalized medicine is defined as a transformative approach that tailors treatment strategies according to individual patient characteristics and genetic profiles. Despite recent advancements in diabetes care, many patients experience therapy failures and diabetes-related complications, necessitating the need for personalized care. The concept of precision medicine, defined by the EASD and the ADA, integrates multidimensional data to optimize diabetes prevention, diagnosis, treatment, and prediction.(Franceschi, 2022) This approach aims to enhance patient care by utilizing genetic information and environmental factors to inform treatment decisions (Chung et al., 2020). Advancements in technologies, including CGM systems, provide real-time data to tailor personalized adjustments to insulin therapy. This approach reduces the risk of hypoglycemia, ensuring the safety of the patient (F. N. U. Sugandh et al., 2023). Additionally, by identifying responders, non-responders, and patients at higher risk of adverse outcomes, a personalized approach optimizes therapeutic outcomes and reduces the rate of treatment failures. Ongoing research in pharmacogenomics has identified specific genetic variants associated with heterogeneous responses to anti-diabetic medications (Kleinberger & Pollin, 2015). This information can guide treatment decisions, enabling physicians to select medications that are more likely to be effective for individual patients (Fitipaldi et al., 2018). In a nutshell, the current knowledge of precision medicine combined with more intensive research in the future, might be paradigm-shifting in diabetes care. It has the potential to revolutionize treatment strategies and improve long-term outcomes in patients with diabetes.

B. Targeting Novel Pathways and Therapeutic Targets

In recent years, significant advancements have been directed toward identifying novel molecular targets to overcome the limitations encountered with existing treatment options. This extensive research has led to the discovery of newer targets such as PPARs, melatonins, glucose-dependent insulinotropic peptides (GIP) receptors, and several novel combinations of already marketed agents (Kanwal et al., 2022). Tirzepatide, a novel dual GLP-1 and GIP agonist, has recently

demonstrated encouraging glycaemic control along with body weight reduction in the SURPASS trial.(Min & Bain, 2021) It has a half-life of nearly 5 days, allowing once-weekly administration.(Frias et al., 2020) Similarly, many other novel combinations including amylin/GLP-1 dual receptor agonists, GIP/glucagon/GLP-1 triple receptor agonists, and a non-peptide oral GLP-1 receptor agonist (orforglipron) are currently under preclinical/early clinical studies (Chong et al., 2024).

Recent targets:

1. Melatonin: Melatonin, is a neuroendocrine hormone, produced by the pineal gland. Apart from its primary physiological functions, it has been found to have an impact on insulin release and regulation of glucose levels in the body (Yeğin et al., 2009). It exerts these actions by binding with melatonin receptors MT1 and MT2 (Owino et al., 2016). Recent preclinical studies have highlighted that MT1 knockout mice exhibited increased insulin resistance (Mühlbauer et al., 2009). These findings hint towards exploiting MT1 as a potential target for patients with diabetes. A study by Reutrakul et al. reported that the administration of melatonin in diabetic patients with lower levels of circulating melatonin improved insulin secretion (Reutrakul et al., 2018).

2. Free fatty receptor-1 (FFA-1): FFA-1 receptors belong to the class of G-protein coupled receptors (Khan & He, 2017). They are located in intestinal cells, pancreatic cells, and taste buds (Roberts et al., 2019). Recent evidence suggested that these receptors influence glucose and lipid metabolism along with the enhancement of insulin secretion (Alquier et al., 2009). The development of drug molecules targeting this class of receptors might yield a novel therapeutic alternative for diabetes care.

3. 11ß-hydroxysteroid dehydrogenase type 1 (11ß-HSD1): This enzyme is responsible for the conversion of inactive cortisone to active cortisol (Chapman et al., 2013). Elevated levels of active cortisol in the body can lead to glucose intolerance, but maintaining optimal levels of 11ß-HSD1 might improve insulin sensitivity.(Berthiaume et al., 2007) Several studies in animal models have demonstrated that a lack of 11ß-HSD1 results in improved glucose tolerance and enhanced insulin sensitivity (Zhang et al., 2009). Thus, inhibition of this enzyme can provide a novel approach to diabetes care.

Several other novel targets namely ACRP-30, FETUIN-A, Visfatin, Metrnl, pigment epithelial-derived factor (PEDF), Vaspin, and G-protein coupled estrogen receptor (GPER) are currently under investigation (Dhankhar et al., 2023).

C. Evidence-Based Practice in diabetes mellitus:

Evidence-based medicine (EBM) integrates scientific evidence, physician judgment, and individual patient preferences to deliver personalized care to individual patients (Mooradian, 2018). Applying this unique therapeutic concept to diabetic patients challenges the traditional glycaemic goals – no single HbA1c level is appropriate for all patients. As such, we should abandon the theory that HbA1c levels less than or equal to 7% are ‘well-controlled’ and greater than 7% are ‘uncontrolled.’ This acknowledges that not all patients with higher-than-normal HbA1c levels are symptomatic. It provides a broader clinical picture out of the traditional notions

of rigidly adhering to the numerical thresholds (Makam & Nguyen, 2017). These fixed outcomes fail to highlight optimal overall treatment benefits and patients' quality of life. These therapeutic approaches include patients along with the healthcare professionals in the shared therapeutic decision-making (Valencia & Dols, 2021). Practicing EBM encourages treatment decisions by carefully evaluating potential harms and benefits based on the circumstances of each patient (Parks et al., 2017). In summary, EBM has the potential to significantly optimize the therapeutic outcomes along with improvements in the quality of life of individuals with T2DM.

8. Conclusion

The molecular landscape of diabetes management has changed tremendously over the decades and many of the developments in the past years showed huge changes in pharmacological therapies, clinical guidelines, and innovative technologies. Through critical review, it is hoped that the reader will have a better understanding of the complexity of DM where the understanding of its pathophysiology and epidemiology becomes imperative in the shaping of effective treatment strategies. Pharmacological treatments have remained the backbone of diabetes management, offering a wide range of treatment options that suit the varied needs of the individual patient. From basic oral agents to sophisticated insulin regimens and promising emerging therapies, healthcare providers have a vast array of tools to play with in ensuring optimal glycaemic control and the prevention of long-term complications. Finally, this review underscores the remarkable progress that has been made in the course of diabetes management while also highlighting the major challenges that still remain to be conquered and emerging opportunities yet to be seized.

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Authors Contribution

Each author participates and contributes to the data collecting, manuscript preparation, including the creation of tables, figures, and the final manuscript proof.

Conflict of interest statement

The writers affirm that there is no conflict of interest.

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