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Beyond Conventional Methods: Exploring New Avenues in Diabetes Care

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Abstract: Diabetes mellitus poses a significant threat to individuals of all ages, disrupting daily life functions. Despite the availability of various synthetic antidiabetic medications and insulin, there is a growing need for new antidiabetic treatments due to adverse effects and the development of resistance to existing drugs over time. This extensive investigation seeks to contribute to the ongoing discourse on diabetes therapies by synthesizing existing research. This review aims to provide clinicians, researchers, and policymakers with a comprehensive understanding of the disease background and the specific pharmacological details of GLP-1 receptor agonists, SGLT2 inhibitors, and other related treatments. The goal is to assist them in developing more effective and personalized strategies to tackle the complex challenges presented by diabetes.

Keywords: Diabetes, Novel therapeutics, Antidibetic treatment, GLP-1 receptor agonists, SGLT2 inhibitors

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Introduction

The characteristic of diabetes mellitus (DM) is hyperglycemia. DM is a chronic metabolic disease that is commonly associated with obesity, hyperlipidemia, hypertension, and cardiovascular diseases, among other chronic problems. Consequently, diabetes is growing in importance as a global health concern. Type 1 diabetes (T1D) and type 2 diabetes (T2D) are the two main forms of diabetes that exist today (Fig. 1). Both environmental and genetic factors may have an impact on the pathophysiology of each type of diabetes (Skyler *et al*., 2017). The chronic ailment known as insulin-dependent diabetes, or T1D, is caused by the loss of β-cells, which results in elevated blood glucose levels because β-cells are not able to produce enough or any insulin. Type 2 diabetes (T2D) accounts for more than 90% of all instances of diabetes and is characterised by insulin resistance and different degrees of β-cell dysfunction. Obesity and this ailment are frequently linked. Living conditions and lifestyle changes have played a crucial role in the recent

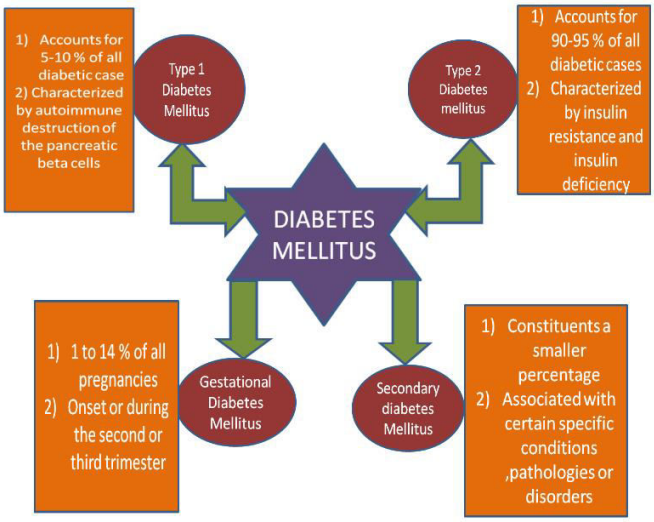

Fig. 1: Types of diabetes mellitus.

decades-long rise in the incidence of diabetes mellitus and its consequences. It was predicted that 451 million individuals globally, or 8.4% of the adult population, received a diagnosis of diabetes mellitus in 2017; by 2045, this number is expected to rise to 693 million (Cho *et al*., 2018). Particularly in low- and middle-income nations, a high frequency of DM has a detrimental social and economic impact. Thus, in order to stop the sharp rise in the prevalence of diabetes mellitus and its complications, preventative and control initiatives are desperately needed. Governments thus continue to enact laws that are simple for those who have DM.

Pathophysiology of diabetes

Diabetes can be classed into four main forms or categories: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and diabeteduced or associated with particular illnesses, pathologies, and/or syndromes. T1DM, formerly known as juvenile-onset diabetes, insulin-dependent diabetes mellitus (IDDM), or type 1A diabetes, accounts for 5–10% of all cases of diabetes. In this autoimmune condition, T-cells attack and destroy pancreatic β-cells, resulting in insufficient insulin production and ultimately hyperglycemia (Knip and Siljander, 2008; Kahaly and Hansen, 2016). Genetic and environmental factors have been found to have an impact on this autoimmune, even though its pathogenesis is still unknown. The majority of instances involving this pancreatic β-cell-specific autoimmunity and the illness itself have a juvenile onset, which is defined as having a rapid onset comparable to that of infants and children. However, they can also develop gradually, similar to adulthood (known as late onset). Variations in immune-mediated pancreatic β-cell mortality rate often dictate the final course of this disease. Diabetic ketoacidosis (DKA), often known as the first indicator of the illness, can occur in some cases, especially in adolescents and teenagers, due to the rapid loss of β-cells and their final collapse. In a small number of cases, the condition advances very slowly and fasting blood glucose levels only slightly increase. Only in the presence of physiological stressors, such as life-threatening illnesses or the onset of additional maladies, does this condition become severely hyperglycemic, with or without ketoacidosis. β-cells may only be able to secrete the minimum quantity of insulin required to prevent ketoacidosis in some other situations, such as adulthood for a considerable amount of time. Nevertheless, as eventually, those who are impacted become significantly or totally insulin deficient and need insulin therapy to survive. Low or undetectable plasma C-peptide

levels are the hallmark of a severe or complete insulin insufficiency, regardless of age (Knip and Siljander, 2008; Kahaly and Hansen, 2016; Skyler *et al*., 2017).

Type-2 diabetes mellitus

As per the former nomenclature, T2DM, sometimes referred to as adult-onset diabetes or non-insulin-dependent diabetes mellitus (NIDDM), accounts for approximately 90–95% of all cases of diabetes. The two primary insulin-related abnormalities that define this kind of diabetes are β-cell malfunction and insulin resistance (DeFronzo, 2004; Leahy, 2005). A reduced sensitivity or reaction of cells in peripheral tissues, specifically the muscle, liver, and adipose tissue, to insulin is the cause of insulin resistance. This is caused by disruption of multiple cellular pathways. In the initial phases of the condition, lowered insulin sensitivity sets off β-cell hyperfunction, which results in an increase in insulin secretion as a compensatory measure to preserve normoglycemia. Thus, hyperinsulinemia, or larger amounts of circulating insulin, prevents hyperglycemia. But over time, the β-cells' enhanced release of insulin is unable to adequately make up for the situations like those linked to infections or other pathological situations. Atypical antipsychotics (drugs classified as second-generation antipsychotics), corticosteroids, and sodium-glucose co-transporter-2 (SGLT2) inhibitors are among the medications that might cause DKA (Fadini *et al*., 2017). Patients with type 2 diabetes frequently do not need insulin therapy at the beginning of the disease or even later in life, provided there are no significant physiological stressors present.

Gestational diabetes mellitus

A diagnosis of diabetes mellitus, commonly in the second or third trimester, at any point during pregnancy is referred to as gestational diabetes mellitus (GDM). Any undiscovered T2DM that may start before or happen at the time of pregnancy beginning was also included in the previous definition. Nevertheless, the most recent guidelines from the International Association of the Diabetes and Pregnancy Study Groups remove diabetes that was discovered during or after pregnancy from this definition in high-risk cases, such as obesity, where any degree of glucose intolerance is referred to as overt diabetes rather than previously diagnosed GDM. In women who are pregnant, GDM is distinct from any underlying diabetes and typically goes away quickly following delivery or pregnancy termination. Early in pregnancy, blood glucose levels are typically lower than normal for both fasting and postprandial periods. However, throughout the third trimester, blood glucose levels rise, and when this happens, the disease is known as gestational diabetes mellitus (GDM). GDM is the cause of more than 90% of diabetes cases and related complications that arise during pregnancy. Between 1% and 14% of pregnancies have GDM, and the populations being studied have a significant impact on the prevalence of the condition. GDM is more common in some racial or ethnic groups than in others, and it has long been known that ethnicity has a significant impact on GDM risk. Asian Indians have the highest prevalence of GDM, as do Aboriginal Australians, Middle Easterners (Lebanese, Syrian, Iranian, Iraqi, or Afghan), Filipinas, people from Pacific Islands, and women from China, Japan, Korea, and Mexico. Black people and non-Hispanic white women have lower prevalence rates (Hedderson *et al*., 2010). The following factors raise the risk of GDM: advanced age, obesity, large-baby pregnancies in the past, and any prior history of GDM or impaired glucose tolerance (Noctor *et al*., 2016). Moreover, a higher lifetime risk of developing type 2 diabetes has been linked to GDM. Therefore, in order to assure early identification of T2DM in such individuals, routine lifelong screening for any form of glucose impairment is strongly advised (Aroda *et al*., 2015).

Treatment for diabetes

Medical nutritional therapy in diabetes

A licenced dietitian nutritionist offers nutrition-based treatment, which is known as medical

nutrition therapy (MNT). It includes nutritional diagnostics as well as therapeutic and expert counselling services to help with diabetes management. MNT is essential to managing and educating people with diabetes. International collaborative groups for diabetes treatment have attempted to reform and offer courses for adverse nutritional transition in their recommendations on MNT (Viswanathan *et al*., 2017). For example, because of its effect on glycaemia, MNT has been used to treat GDM, where carbohydrate (CHO) is the primary causal agent. Pregnant women need at least 175 g of CHO per day, according to the Institute of Medicine, and low-CHO diets that have long been used to treat GDM have been shown to be safe (Institute of Medicine, 2005). Furthermore, it has been noted that MNT is essential for the treatment of many forms of diabetes mellitus, and as such, it has a substantial effect on patients, particularly women and infants (Moreno *et al*., 2016). MNT mostly works to prevent ketogenesis and metabolic acidosis while maintaining adequate weight gain during pregnancy and foetal growth. However, in terms of calorie content and the distribution, quality, and quantity of macronutrients, among other aspects, MNT has not yet determined the ideal diet for DM. Studies have demonstrated that, when their intake of carbohydrates is specifically considered, the nutritional needs of GDM patients are the same for all cases of pregnancy. Presently, a low-glycemic index diet has been found to be more beneficial in the management of GDM than the conventional intervention of limiting carbohydrates, however, the data is still preliminary. In order to effectively manage overweight or obesity, calorie restriction is essential (Moreno *et al*., 2016).

Need of novel approaches for treatment of diabetes

Type 2 diabetes mellitus is a major threat to health with a prevalence increasing in epidemic proportions. The World Health Organization estimates that by 2030, type 2 diabetes will affect over 360 million people worldwide. Inevitably, diabetes and its complications will strain public health resources.

Despite the availability of many anti-diabetic agents, approximately 60% of patients do not achieve the target glycated hemoglobin (HbA1C) level of ≤7%. Reasons for this include: non-compliance; side-effects of treatments; fear of hypoglycaemia; weight-gain; problems with dose titration of anti-diabetic agents; and more stringent HbA1C targets set by healthcare organisations which tend to change. Clearly, additional therapeutic options are needed that will overcome these clinical shortcomings.

Nanotechnology and diabetes

Using nanoparticles (less than 100 nm) is an aspect of nanotechnology. Individual atoms or molecules within a substance are manipulated to create these nanoparticles. Nanomedicine is the practice of using nanotechnology in medicine. Combining the understanding of nanotechnology with the use of medications or diagnostic compounds to enhance their ability to target particular cells or tissues is known as nanomedicine. Through the use of innovative nanotechnology-based glucose testing and insulin, nanotechnology in diabetes research has improved the results of diabetic treatment in diabetics in a number of ways (Veiseh *et al*., 2014). Nanotechnology is being used to generate more effective vaccines and non-invasive methods of delivering insulin, such as gene- and cell-based therapeutics for type 1 diabetes (Disanto *et al*., 2015). Innovative diabetes diagnosis, the identification of immune cell activity and beta-cell mass, glucose monitoring, non-invasive insulin delivery, and other applications are just a few of the ways that nanotechnology plays a significant role in diabetes care.

Gene therapy and diabetes mellitus

Gene therapy is a technique in which the external normal gene is included to treat the symptoms of a disease caused by a faulty gene. Its benefit is that any condition can be cured with a single treatment, and gene therapy is continuously creating new treatment choices across various medical specialties (Xu *et al*., 2003). These days,

gene manipulation includes gene editing and regulation in addition to gene insertion (Mali, 2013). Another way to conceptualise gene therapy is as a way to introduce a gene or modify an existing gene within a cell to treat an illness (Kaufmann, 2013). This strategy aims to correct aberrant genes that have been identified as the causing agent in any illness and to successfully stop the illness from starting or from getting worse. The gene therapy strategy uses three main forms of intervention: the introduction of a novel gene into the body, swapping out the malfunctioning gene for a functional one, and turning off the genes causing the illness. There are two subtypes of gene treatment: germline gene therapy and somatic gene therapy. In germ-line gene therapy, the goals are the reproductive cells, whereas the main target in somatic gene therapy is the somatic cells, also known as the sick cells. The disease is prevented from spreading to future generations using germline treatment. Because gene therapies have the potential to treat a wide range of conditions that are challenging to treat with traditional medicines, such as diabetes mellitus, autoimmune disorders, heart illnesses, and malignancies, they are being used as trends in emerging therapeutics (Tsokos and Nepom, 2000).

Latest inventions in diabetes mellitus therapy

Tripeptide

The medication was just granted FDA approval to treat type 2 diabetes under the trade name Monaro (FDA-2022). Once a week, a subcutaneous injection called tirzepatide is administered to target hormone receptors that are essential for the metabolism of glucose. These are the hormones known as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). While GLP-1 lowers blood sugar through a variety of ways, including as promoting insulin secretion and inhibiting glucagon release in hyperglycemia, GIP both increases insulin release in hyperglycemia and increases glucagon release in hypoglycemia.

Incretin therapeutics

Incretin-based therapies, designed to emulate the natural effects of glucagon-like peptide 1 (GLP-1), have transformed the management of type 2 diabetes since their introduction to clinical practice in 2006. GLP-1 mimetics have gained popularity among both physicians and patients due to their ability to address several drawbacks associated with existing therapies. They mitigate the risk of hypoglycemia by functioning in a glucose-dependent manner, promote weight loss by slowing gastric emptying and curbing appetite, and suppress glucagon secretion. These mimetics have proven beneficial in filling the treatment gap for patients with poorly controlled diabetes (HbA1c >8%) who have not responded to oral hypoglycemic medications but are hesitant to initiate insulin therapy due to concerns about weight gain and hypoglycemia (Saydah *et al*., 2004).

The two approved GLP-1 analogs, exenatide and liraglutide, are administered via subcutaneous injection. Exenatide has been shown to provide a sustained reduction in HbA1c of 1% over three years, with 46% of patients achieving a target HbA1c of <7%. Comparative studies against metformin, sulfonylureas, and insulin glargine have demonstrated that exenatide yields superior reductions in HbA1c levels (Pratley and Gilbert, 2008).

Liraglutide, in comparative studies, has shown superior reductions in HbA1c compared to glimepiride, metformin, rosiglitazone, and insulin glargine. In a direct comparison with exenatide, liraglutide was associated with a superior reduction in HbA1c of 0.3% (Hansen *et al*., 2010).

GLP-1 agonists have gained even more popularity due to clinical evidence showing their beneficial effects on the adverse cardiovascular profile associated with type 2 diabetes. Exenatide has been linked to various positive outcomes, including an average weight reduction of approximately 5 kg, a 12% decrease in serum triglycerides, a 5% decrease in total serum cholesterol, a 6% decrease in serum low-density lipoprotein cholesterol, a 24% increase in cardio-

protective serum high-density lipoprotein cholesterol, and a significant improvement in hepatic steatosis biomarkers such as alanine aminotransferase, showing a reduction of 41% (Klonoff *et al*., 2008). Similarly, liraglutide has shown comparable benefits, along with achieving a 4% reduction in systolic blood pressure (Hansen *et al*., 2010).

Exenatide is typically associated with dose-dependent side effects such as nausea, vomiting, and diarrhea, which tend to diminish with continued use. While cases of acute pancreatitis have been reported, the estimated incidence is relatively low, ranging from 0.33 to 0.44 per 1000 adults per year (Bain and Stephens, 2008). Recently, the Food and Drug Administration (FDA) issued a safety warning regarding exenatide, linking it to the potential development of ischemic renal failure (Weise *et al*., 2009).

Overall, liraglutide is generally well tolerated, with a lower occurrence of nausea compared to exenatide. Liraglutide has been linked to thyroid hyperplasia and medullary thyroid carcinoma, prompting a 'black-box' warning. However, this association appears to be limited to rodents, and thus far, there is no evidence establishing a causal relationship between liraglutide and medullary thyroid cancer in humans. Phase I trials for an oral form of liraglutide are scheduled to commence soon.

Additional GLP-1 analogs currently in clinical trials feature longer-acting formulations, allowing for once-weekly dosing. Among these are taspoglutide, albiglutide, lixisenatide (also known as AVE0010), and a once-weekly version of exenatide.

Amylin agonists

Amylin agonists possess all the actions of incretins except for stimulating insulin secretion. Pramlintide, the sole licensed amylin analogue, is linked to reductions in HbA1C ranging from 0.5% to 1.0%. The primary adverse effect is typically nausea, which tends to diminish with ongoing treatment (Schmitz *et al*., 2004).

Dipeptidyl peptidase IV inhibitors

The therapeutic effectiveness of endogenous GLP-1 is constrained by its short physiological half-life, primarily due to rapid inactivation by dipeptidyl peptidase IV (DPP-IV). Several DPP-IV selective inhibitors have been developed, including licensed ones such as sitagliptin, vildagliptin, and more recently, saxagliptin. These inhibitors typically achieve a reduction in HbA1c of 0.4% to 0.7% over 12 months and, when used as monotherapy, do not induce hypoglycemia. Common adverse effects include nasopharyngitis and urinary tract infections (Mikhail, 2008). However, the FDA has received reports of 88 cases of pancreatitis associated with sitagliptin therapy. Other DPP-IV inhibitors currently undergoing phase III clinical trials include linagliptin, dutogliptin, gemigliptin, and alogliptin.

Central neurotransmitter modulators

The regulation of body fat stores and insulin function involves the intricate interplay of circadian neuroendocrine rhythms. Bromocriptine acts by modulating neurotransmitter activity in the brain. Research involving bromocriptine in type 2 diabetes has demonstrated enhancements in glycemic control and glucose tolerance, resulting in reductions in HbA1c levels of approximately 0.56% (Gaziano *et al*., 2010). Despite obtaining FDA approval, bromocriptine is not included in the type 2 diabetes management guidelines established by the National Institute for Health and Clinical Excellence.

Experimental agents

The Glimins

Imeglimin, classified as an oxidative phosphorylation inhibitor, represents the inaugural member of a novel category of oral anti-diabetic medications termed - the Glimins. These drugs are designed to address the three primary abnormalities associated with type 2 diabetes: inadequate insulin production, heightened hepatic gluconeogenesis, and compromised glucose uptake by skeletal muscles (Poxel, 2010).

Currently, its effectiveness is under investigation in phase IIa clinical trials.

Renal sodium-dependent glucose co-transporter-2 inhibitors

The renal glucose reabsorption mechanism relies on renal sodium-dependent glucose co-transporter 2 (SGLT2) receptors. Predominantly, the low-affinity, high-capacity SGLT2 receptors situated in the proximal renal tubule facilitate the reabsorption of most filtered glucose. SGLT2 inhibitors enhance the excretion of glucose in urine, leading to reductions in blood glucose levels independent of insulin, resulting in HbA1c decreases ranging from 0.55% to 0.9%. Examples of these inhibitors include remogliflozin, etabonate, sergliflozin, and dapagliflozin (Chao *et al*., 2020).

Fructose 1,6-bisphosphatase inhibitors

The pathophysiology of type 2 diabetes is characterized by an overactive gluconeogenesis process. Recently, there has been interest in the use of selective inhibitors targeting fructose 1,6-bisphosphatase, a key enzyme controlling gluconeogenesis. However, existing evidence demonstrating glucose-lowering effects is currently restricted to studies conducted in rodents (Van Poelje, 2006).

Peroxisome proliferator-activated receptor α/γ ligands

The potential of peroxisome proliferator-activated receptor (PPAR) agonists to mitigate cardiovascular risk in type 2 diabetes remains an area of ongoing interest. In the SYNCHRONY trial, aleglitazar demonstrated reductions in HbA1c ranging from 0.36% to 1.35%, along with improvements in adverse lipid profiles associated with high risk. Subsequently, it has progressed to phase III clinical trials. However, there are apprehensions regarding PPAR α/γ ligands. Two such agents, muraglitazar and tesaglitazar, were withdrawn due to concerns about their association with significant cardiovascular events (Henry *et al*., 2009).

MBX-2982

G-protein coupled receptor 119 (GPR119) is a receptor located in both the gut and pancreas, which interacts with bioactive lipids to trigger glucose-dependent incretin and insulin secretion. MBX-2982, an agonist of GPR119, has successfully completed three phase I clinical trials, consistently demonstrating significant reductions in glucose levels with clinical significance. It has now progressed to phase II clinical trials (Metabolex, 2010).

Conclusion

The advancement of diabetes management extends beyond pharmaceutical interventions, necessitating a holistic understanding of patient needs, integration of digital health solutions, and the pursuit of tailored, precise treatments. As we navigate this evolving landscape, it becomes evident that the future of diabetes care hinges not only on achieving glycemic control but also on enhancing overall health, minimizing complications, and elevating the quality of life for individuals with diabetes. This shift in focus requires a departure from conventional metrics towards a comprehensive, patient-centered approach to care. The insights gained from this exploration underscore a critical juncture where the imperative for further research is paramount. Areas identified for further investigation, including deepening our understanding of novel therapies, developing individualized treatment strategies, evaluating treatment efficacy in real-world contexts, and integrating digital health solutions, present an opportunity for collaboration among researchers, clinicians, and policymakers to shape the trajectory of diabetes research. The diabetes research community holds the key to a future where innovative therapies seamlessly integrate into practice, guidelines evolve dynamically, and personalized care becomes the cornerstone of diabetes management. Embracing interdisciplinary collaboration, attuning to patient needs, and fostering a culture of continual learning are vital for realizing this vision.

In summary, achieving optimal diabetes care requires ongoing dedication, collaboration, and an unwavering commitment to enhancing the well-being of those affected by diabetes. As we embark on this journey, the integration of knowledge, application of research in clinical settings, and cultivation of a patient-centric mindset serve as guiding principles, illuminating the path forward in the ever-evolving field of diabetes care.

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