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**Analysis of the management and therapeutic performance of diabetes mellitus
employing special target**

Sun HY *et al.* Diabetes management: Special targets analysis

Abstract

Diabetes mellitus (DM) is a chronic metabolic condition characterized predominantly by hyperglycemia. The most common causes contributing to the pathophysiology of diabetes are insufficient insulin secretion, resistance to insulin's tissue-acting effects, or a combination of both. Over the last 30 years, the global prevalence of diabetes increased from 4% to 6.4%. If no better treatment or cure is found, this amount might climb to 430 million in the coming years. The major factors of the disease's deterioration include age, obesity, and a sedentary lifestyle. Finding new therapies to manage diabetes safely and effectively without jeopardizing patient compliance has always been essential. Among the medications available to manage DM on this journey are glucagon-like peptide-1 agonists, thiazolidinediones, sulphonyl urease, glinides, biguanides, and insulin-targeting receptors discovered more than 10 years ago. Despite the extensive preliminary studies, a few clinical observations suggest this process is still in its early stages. The present review focuses on targets that contribute to insulin regulation and may be employed as targets in treating diabetes since they may be more efficient and secure than current and traditional treatments.

Key Words: Diabetes mellitus; Hyperglycemia; Therapeutic performance; Management; Special target; Literature review

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Core Tip: Diabetes mellitus (DM) is a chronic metabolic condition characterized predominantly by hyperglycemia. The most common causes contributing to the pathophysiology of diabetes are insufficient insulin secretion, resistance to insulin's tissue-acting effects, or a combination of both. Over the last 30 years, the global prevalence of diabetes increased from 4% to 6.4%. If no better treatment or cure is found, this amount might climb to 430 million in the coming years. The major factors of

the disease's deterioration include age, obesity, and a sedentary lifestyle. Finding new therapies to manage diabetes safely and effectively without jeopardizing patient compliance has always been essential. Among the medications available to manage DM on this journey are glucagon-like peptide-1 agonists, thiazolidinediones, sulphonyl urease, glinides, biguanides, and insulin-targeting receptors discovered more than 10 years ago. Despite the extensive preliminary studies, a few clinical observations suggest this process is still in its early stages. The present review focuses on targets that contribute to insulin regulation and may be employed as targets in treating diabetes since they may be more efficient and secure than current and traditional treatments.

INTRODUCTION

Mellitus, short for "sugar disease", pertains to the endocrine conditions known as diabetes. Diabetes mellitus (DM), one of the most common conditions, is presently the seventh leading cause of death, with 5.2 million deaths worldwide^[1]. Diabetes that is either untreated or poorly managed is thought to be the cause of 1.5 million deaths annually globally. From 108 million cases (4.7%) in 1980 to 425 million patients (8.5%) in 2017, it is expected that 629 million people will have diabetes by 2045. The cost of treating diabetes worldwide is predicted to be 760 billion USD per year, with costs being the same for men and women^[2]. Both inadequate insulin production by the pancreas or elevated glycosylated hemoglobin and improper insulin response by bodily cells contribute to the development of DM^[3]. In addition, the development of diabetes can be influenced by a wide variety of factors, including a lack of physical activity, excessive consumption of food and beverages, obesity, stress, and industrialization. Environmental and genetic factors are the primary causes of diabetes^[4]. Diabetes can cause many health problems if not treated, such as chronic hyperglycemia, which can cause long-term damage to the blood vessels, heart, eyes, nerves, kidneys, and other organs^[5].

4 Diabetes is classified into three types: Type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes (GD), and other variants. T1D affects approximately 5%-10% of

individuals diagnosed with it, usually young children and teenagers^[6]. A complete lack of insulin production brings on type 1 DM (T1DM). Type 2 DM (T2DM), which is much more common, is caused by inadequate corrective insulin secretory response and resistance to insulin action^[7]. 90%-95% of people with diabetes have T2DM, the most common type, which continues to increase worldwide^[8]. In the 20 years following delivery, GD increases the chance of T2D by 35%-60%. One in every six live births is complicated by GD, which occurs in the second or third trimester of pregnancy^[8]. Drug-induced diabetes, pancreatic illness, and monogenic diabetes are additional types. Type 1.5 diabetes, also known as latent autoimmune diabetes in adults (LADA), is like T2DM, which occurs gradually throughout development. LADA is an autoimmune disease that cannot be treated by modifying an individual's diet or lifestyle^[9].

The proportion of the aging population is increasing, and this trend is explained by urbanization, socioeconomic growth, highly processed diets, and a decline in physical exercise. Untreated diabetes typically causes unintentional weight loss, increased excretion, increased thirst, and increased appetite^[10]. T1DM symptoms can appear suddenly, whereas T2DM symptoms typically appear much more gradually and may even be nonexistent. About half of the people do not realize they have T2D because there are few symptoms or signs in the early stages of the disease. As a result, symptoms go undetected and lead to complications associated with diabetes^[11]. Glycated hemoglobin (HbA1C), fasting plasma glucose level (126 mg/dL), and plasma glucose (200 mg/dL) tests are used to identify DM. Nowadays, there is no validated prophylactic method for T1DM. By maintaining a healthy body weight, getting exercise, and adhering to a wholesome diet, T2DM can be prevented. Higher levels of physical activity (> 90 min/d) reduce diabetes risk by 28%^[11].

Diabetes management aims to keep blood sugar levels near normal without lowering them. This is usually accomplished by making dietary changes, exercising, losing weight, and taking the appropriate medicines. Restoring normal carbohydrate metabolism is the primary aim of DM management and control^[12]. Insulin replacement therapy is needed for people with total insulin deficiency. Contrarily, nutritional

1 changes and exercise can be used to treat insulin resistance. Preventing or treating the numerous complications that can arise from the illness and its treatment are other objectives of diabetes management^[12]. This review aims to analyze the management and therapeutic performance of DM using specific targets. Our current comprehensive study has identified several potential targets with promising leads that, if further explored, may result in developing the next wave of anti-diabetic medications.

DM PATHOPHYSIOLOGY

Several hormones cooperate to maintain an appropriate amount of glucose in the body. However, two hormones, insulin and glucagon, dominate in regulating glucose homeostasis. When the level of glucose increases, cells in the pancreatic islets of Langerhans produce insulin. Insulin lowers blood sugar levels by preventing the liver's synthesis of glucose through glycogenolysis and gluconeogenesis^[13] or by boosting the liver, muscle, and fat tissues' glucose uptake, except for soft muscle, where insulin functions *via* insulin-like growth factor-1. Therefore, all types of DM are caused by insulin deficiency or receptor insensitivity. Insulin has the following effects: Decreasing gluconeogenesis and inhibiting gluconeogenesis, promoting glucose transport into adipose and muscle cells, and raising glycogen storage^[14].

Fewer beta cells produce insulin when glucose levels are low, and less glycogen is converted into glucose. The pancreatic cells secrete glucagon. By accelerating liver functions like glycogenolysis and gluconeogenesis, glucagon enhances the effects of insulin. The cells that require glucose are unable to absorb it, and it is not stored correctly in the liver and muscles if there is not enough available insulin, if cells are resistant to the effects of insulin (insulin resistance), or if the insulin itself is defective^[15]. Consistently high blood glucose levels, impaired protein synthesis, and metabolic anomalies like metabolic acidosis are the results of severe insulin deficiency. Maintaining a high blood glucose level causes the kidneys to reach their reabsorption limit, resulting in the excretion of excess glucose through urine (glycosuria). This leads to polyuria and fluid loss because the osmotic pressure of the urine goes up, and the

kidneys take in less water^[16]. Dehydration and increased thirst (polydipsia) result from the body osmotically replacing blood volume with water from other sources, such as cells and different bodily compartments.

Additionally, low glucose levels in the blood increase hunger, leading to overeating (polyphagia)^[17]. Cortisol and catecholamines also raise plasma glucose levels in addition to glucagon. Glucose-dependent insulintropic polypeptide, glucagon-like peptide-1 (GLP-1), and amylin are additional hormones that help to maintain an average blood glucose level [glucose-dependent insulintropic polypeptide (GIP)]^[18].

Along with insulin, amylin is released. It lessens stomach emptying, improving glucose absorption following a meal. Incretins or peptides produced from the gut include GLP and GIP. These incretins help the pancreatic beta cells produce and secrete insulin^[19]. Neither the intestine nor cells in need of energy can easily absorb glucose. Therefore, glucose transporters are responsible for delivering glucose to the cells. Sodium-glucose co-transporter (SGLT) and facilitative glucose transporter are two examples of the two kinds of glucose transporters, which are a family of membrane-bound glycoproteins (GLUT)^[20]. The interplay of genetic and environmental factors largely determines T2D. The risks increase with increasing levels of overweight or obesity. Hormonal changes that arise during pregnancy are the cause of GD. Hormones produced by the placenta lessen the sensitivity of cells to the impacts of insulin. DM can result from genetic mutations like a single gene mutation that can produce monogenic diabetes^[21].

The most common forms of monogenic diabetes or maturity-onset diabetes of the young are diabetes at birth and diabetes that develops in early adults. Thick mucus is produced by cystic fibrosis, which prevents the pancreas from producing enough insulin, leading to pancreatic scarring. The body stores an excessive amount of iron due to hemochromatosis. Iron can accumulate in the body and harm other organs, including the pancreas, if the condition is not treated^[20]. High hormone production levels in the body are a symptom of some hormonal illnesses, which can lead to insulin resistance and diabetes in some people. Excessive levels of cortisol, also known as the stress

hormone, cause Cushing's syndrome^[21]. Too much growth hormone causes acromegaly^[22,23]. When the thyroid gland generates too much thyroid hormone, hyperthyroidism develops. Diabetes is caused by pancreatic damage or removal, including pancreatitis, pancreatic cancer, and trauma. These conditions have the potential to cause harm to β -cells or decrease their ability to produce insulin. Diabetes develops if the damaged pancreas is removed due to β -cell loss^[24] (Figure 1).

MANAGEMENT OF DM

Diabetes management aims to boost output and quality of life for people with diabetes by: (1) Early detection; (2) Long-term and short-term morbidity prevention; (3) Early death prevention are all examples of early diagnosis^[25]; (4) Supporting diabetes patients' freedom and self-care habits; (5) Reduction of the personal, family, and societal burden of diabetes; and (6) Achieving these objectives depends on the facilities and diabetes health care team being successfully established. This involves educating those with diabetes and healthcare professionals^[26].

Blood sugar level

¹ A glucose meter is used to test blood sugar levels, and the results are displayed either in mg/dL or mmol/L of blood. A healthy individual's average fasting glucose level is 4.5 mmol/L (81 mg/dL), ranging from 65 to 98 mg/dL at its lowest and highest points, respectively^[27]. The most effective method to manage diabetes is for each patient to keep track of their blood glucose levels and how exercise and food affect them. Patients can improve their diabetes management by changing their habits^[28].

Hypo and hyperglycemia

A hypoglycemic episode is a glucose level of 3.8 mmol/L. 55% of cases of severe hypoglycemia occur during sleep in T1D that is well-controlled. 6% of fatalities in people with diabetes under 40 are attributed to nocturnal hypoglycemia (dead-in-bed syndrome)^[29]. According to the National Institute of Health data, hypoglycemia

accounts for 2% to 4% of all diabetic deaths. After intensive glucose control, 21% of hypoglycemia incidents in children and adolescents were unexplained. In addition to being fatal, hypoglycemia can also cause cerebral damage during severe episodes. Although glucose is typically linked to diabetic nerve disease, hypoglycemia can also start or exacerbate neuropathy in people with diabetes who are actively trying to lower their hyperglycemia^[30]. It is essential to carefully monitor levels above 230-270 mg/dL, regarded as high and should be brought down rather than allowed to stay high. Hyperglycemia is the term for high blood sugar levels, which is harder to spot than hypoglycemia and typically develops over days instead of hours or minutes. If unattended, this may cause a diabetic coma and mortality^[31].

Glycemic control

In medicine, the word "GC" refers to the typical blood sugar levels of a person with DM. Numerous pieces of evidence indicate that years of hyperglycemia cause multiple serious issues of diabetes, especially complications of microvascular origin. Effective glycemic control (GC), in the sense of a "target" for treatment, has become a crucial aim of diabetes care despite recent research suggesting that genetic factors may be accountable for the complications of diabetes^[32]. T1D is brought on by the autoimmune condition that first rendered the pancreas incapable of making insulin. Because blood sugar levels vary throughout the day and glucose records are unreliable indicators of these changes, the quantity of HbA1C is a substitute indicator of long-term GC in research studies and clinical therapy for people with diabetes^[33].

The hemoglobin A1c test, or HbA1C, measures the average glucose levels over the two to three months prior. By the most popular measures, HbA1C is typically 4%-6% in non-diabetic individuals with average glucose metabolism. Blood glucose and HbA1C levels of 11-28 mmol/L and 9%-15% or higher, respectively, over months and years before severe complications develop, are indicative of poor GC^[34]. There has been no difference in all-cause mortality, nonfatal stroke, or limb amputation in extensive studies comparing the impact of strict GC to conventional or more relaxed GC in T2D.

Still, there has been a 15% decrease in the risk of nonfatal coronary artery disease^[35]. Despite being linked to a 2.4-fold higher risk of hypoglycemia, strict glucose control is also related to a lower risk of retinopathy and nephropathy and a lower incidence of peripheral neuropathy^[36].

Personal glucose monitoring

Regular home glucose meter use by patients, especially those with T1D, may improve management and outcomes for both type 1 and 2 diabetes. Keeping tabs on one's glucose levels is time-consuming and labor-intensive, not to mention costly. Monitoring blood glucose levels helps keep the illness under control and lessen the likelihood of serious complications later on^[37]. There are many different kinds of blood monitoring devices, and each one works for every patient. For those with T1D, self-testing is crucial because insulin therapy can result in low blood sugar (hypoglycemia), and home testing allows you to adjust the dosage each time you administer insulin. A new study suggests that self-monitoring does not improve blood glucose control or quality of life, even though its efficacy in T2D has been more controversial. Despite home blood glucose monitoring, type 2 patients are considered to have poor long-term management^[38].

Continuous glucose monitoring (CGM) technology has improved to provide data regarding the pace and pattern of glucose changes in people with diabetes. The accuracy of these devices is improving with each new advancement, although self-monitoring blood glucose calibration remains necessary and is not designed for correction boluses^[39]. The CGM and Libre Sensor are used in the Libre Blood Sugar Diet Program, and by collecting all data via smartphone and smartwatch, experts can evaluate it in real-time, round-the-clock, every day of the week. As a result, certain foods can be determined to raise blood sugar levels, while others can be identified as being healthy and not doing so. Sugar is absorbed differentially by each individual, so testing is necessary^[40].

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HbA1c test

The measurement of blood HbA1c levels is a valuable test typically performed in a laboratory. This is the proportion of HbA1C to overall hemoglobin. The percentage of these molecules increases as plasma glucose levels remain elevated. This test, once thought to assess the average level of diabetic control over about three months, has been suggested to emphasize the most recent 2 to 4 wk^[41]. HbA1c levels range from 4.0 to 6.0 in people who don't have diabetes. People with diabetes whose HbA1c levels stay < 6.5% are said to have reasonable GC^[37]. ¹ If diet or treatment adjustments have been made within the last six weeks, or if there is a hemoglobinopathy or a disruption in red cell aging, the HbA1c test is inappropriate. The alternative Fructosamine test shows standard control over the previous two to three weeks^[42].

Use of digital tools

People with T2DM can lower their blood sugar levels by sharing their electronic health data with them. It is a method of assisting individuals in understanding their health conditions and actively participating in their administration. About 100000 health-related apps are available on Google Play and the App Store, and the most general category is diabetes applications^[43]. Routine self-management activities such as taking medication and insulin, monitoring blood sugar levels, adhering to a diet, and participating in physical exercise present significant challenges. Nevertheless, despite the many applications available, only a relatively small percentage of patients use them^[44].

Furthermore, a 2016 study of 65 Android diabetes apps discovered that confidential information, such as insulin and blood sugar levels, “was routinely collected and shared with third parties”. One study investigates how a T2D Android mobile application can integrate supporting hardware such as an exercise bike, a treadmill, a heart-rate sensor, a wearable band, and a glucometer. This mobile program includes drugs, food consumption, exercise, and sleep tracking. Adesina *et al*^[45] examine the effectiveness and applicability of digital tools designed to assist women with GD dietary self-management.

Foot examination

The likelihood of diabetic foot ulcers can be predicted by keeping an eye on a person's feet. A standard method is using a specialized thermometer to check for hotspots on the foot that could be signs of an ulcer. However, there is scant reliable research on the benefits of tracking foot temperature at home^[46]. This technique is intended to supplement, not replace, people who regularly check their feet^[47].

LIFESTYLE MANAGEMENT

Diet

A healthy diet with some carbohydrates; over time, consuming a consistent quantity of carbohydrates is beneficial to help T1DM patients better control their blood sugar levels. There is insufficient proof that low-carbohydrate diets benefit individuals with T1D^[48]. However, it may be possible for some people to follow a low-carbohydrate diet and carefully manage their insulin doses^[49].

Exercise

In addition to lowering blood sugar levels, exercise can increase insulin sensitivity and lower the chance of diabetes-related heart disease^[50]. Numerous studies have demonstrated that exercise aids glycemic management and reduces HbA1c levels by about 4.2 mmol/mol (0.6%). Studies have shown that individuals with T2D who participate in both physical activity and dietary changes have a lower risk of developing impaired glucose tolerance^[51]. Physical activity has an impact on T1D glucose management in that near-exercise energy expenditure rises to account for possible hypoglycemic episodes; this may help to explain why blood glucose levels do not fall during exercise. Exercise increases the translocation and expression of glucose transporter type 4 (GLUT4). This insulin-regulated glucose transporter provides glucose to muscle and adipose cells, making those with T1D more susceptible to nocturnal hypoglycemic episodes^[52]. Although exercise may not directly lower blood glucose

levels in people with T1D, many benefits remain, such as reduced risk of cardiovascular diseases, improved insulin sensitivity, blood pressure, body composition, lipid profiles, and endothelial function^[53].

Medication

The vast majority of drugs for diabetes work ⁷ by lowering blood sugar levels in various ways. There is widespread consensus that people with diabetes who maintain tight glucose control and keep their blood glucose levels within normal limits have fewer complications, such as kidney or eye problems. Several distinct types of anti-diabetic medications^[54]. A “basal-bolus” regimen that most closely mimics natural insulin release is optimal for treating T1D: Long-acting insulin for the basal rate and short-acting insulin with food^[55]. Most people with T2D are treated with oral medications, though some ultimately need to be treated intravenously with insulin or GLP-1 agonists. Metformin is usually recommended as the initial therapy for T2D because there is strong evidence that it lowers mortality rates. Furthermore, it decreases the volume of glucose produced in the liver while increasing the quantity of glucose retained by peripheral tissue^[56].

THERAPEUTIC PERFORMANCE OF DIABETES MILLETUS EMPLOYING SPECIAL TARGETS

Even though biomedicine has made a lot of progress and we are learning more and more about how to treat different diseases, diabetes is still hard to treat. To solve this problem, researchers from various fields are looking for a way to treat diabetes that is both safe and easy^[57]. In addition, rigorous evaluation of the drug action mechanisms of known compounds is beneficial for further validating several novel molecular drug targets.

In contrast to several extant synthetic medicines, natural biomolecules have a wide range of structural variability and have emerged as a valuable source of active agents for developing newer lead compounds in drug discovery^[58]. Anti-diabetic medications

like dipeptidyl peptidase 4, thiazolidinedione, sulfonylurea, or metformin inhibitors are currently used to treat DM. However, these drugs cannot entirely limit diabetes, and future studies are required to find a better cure^[59].

In biological systems, receptors are chemical structures composed of proteins that receive and transmit signals. These are some of the receptors and medications that are currently used to treat diabetes, including thiazolidinediones, gliptins, GLP-1, glinides, biguanides, insulin, peroxisome proliferator-activated receptors (PPARs), sulphonylureas, β -glucosidase inhibitors, amylin mimics, SGLT-2, and dopamine D-2 agonists^[60]. Pro-hormone convertases (PC 1 and PC 2) and exo-protease carboxypeptidase make insulin from pro-insulin. These enzymes produce insulin and C-peptide^[61]. Insulin facilitates the translocation of GLUT4 to the cell, causing adipose/skeletal muscle cells to consume additional glucose. Other cutting-edge candidates for managing DM include components of G protein-coupled receptor (GPCR) 119, G protein-coupled estrogen receptor (GPER), vaspin, metnrl, pigment epithelium-derived factor (PEDF), GPCR, GIP, melatonin (MLT), visfatin, ACRP 30 (AdipoQ), and fetuin-A^[60,62].

Exenatide and liraglutide are two examples of GLP-1 analogs that replicate the effects of endogenous GLP-1. They contribute to better blood glucose control and weight management by increasing glucose-dependent insulin secretion, decreasing glucagon secretion, delaying stomach emptying, and promoting satiety^[63]. Recent randomized controlled trials have shown that T2D patients who consume GLP-1 analogs experience significant weight loss and a significant drop in HbA1c levels. Liraglutide, for instance, was associated with a 13% relative risk decrease in major cardiovascular events, according to the LEADER trial^[64]. Frequently observed adverse effects encompass gastrointestinal issues, while ongoing investigations are being conducted to ascertain the long-term safety implications, particularly concerning pancreatitis and thyroid cancer^[65].

PPARs, especially PPAR-gamma agonists like pioglitazone, regulate glucose and lipid metabolism and increase insulin sensitivity in peripheral tissues. In diabetic

patients, PPAR-gamma agonists have decreased insulin resistance, lowered HbA1c levels, and minimized cardiovascular risk^[66]. The administration of pioglitazone has been correlated with weight gain and elevated susceptibility to heart failure, necessitating the meticulous selection of patients^[67].

Although vaspin has gained attention recently, its therapeutic applications are not as well established as those of GLP-1 and PPARs. Several investigations have indicated changes in vaspin levels in individuals with diabetes. However, the precise therapeutic consequences of these alterations have not been completely clarified^[68]. Further investigation is required to elucidate the mechanisms by which vaspin may be selectively manipulated to provide therapeutic advantages in diabetes. Concurrently, active clinical trials are being conducted to explore this potential. These targets may represent the diabetes treatments of the future (Table 1).

TRADITIONAL PRINCIPLES FOR TREATING DM

Conventional targets are medications used in the market for a while to treat diabetes. Still, their availability is restricted, and they come with several drawbacks, like weight gain, hypoglycemia, and other side effects. They work by keeping the level of glucose in the blood steady. For example, biguanides reduce the amount of glucose produced and increase the amount of glucose used by skeletal muscles and the liver. SGLT-2 antagonists stimulate the kidney's ability to excrete glucose. A-glucosidase inhibitors reduce intestinal uptake of glucose and free fatty acids (FFA). Pancreatic insulin production and sensitivity are both improved by sulphonyl urease. The release of FFA from adipose cells is reduced by 2,4-thiazolidinediones^[32,69].

GOALS RECENTLY ACHIEVED IN DM

MLT

The pineal gland secretes the neuroendocrine hormone MLT at night. MLT has been identified as a possible therapeutic target for treating T2D because it also regulates glucose and the pancreatic release of insulin. It exerts its pharmacological effects by

interacting with the MT1 and MT2 MLT receptors^[70]. Recent research has revealed that mice lacking the MLT MT1 receptor exhibit increased insulin resistance and glucose intolerance. MLT's MT1 receptor is an important therapeutic target for controlling blood sugar levels^[71].

PPARs

Transcription factors control gene expression called PPARs, of which there are three types: PPAR α , PPAR γ , and PPAR β/δ ^[72]. Thiazolidinediones, PPAR-agonists, turn on the receptor, making the body more sensitive to insulin. After being turned on, they lower the levels of FFA in the blood and change the levels of adipokines. This is possible by increasing insulin release from the pancreas, improving glucose intake in skeletal muscle and adipose tissues, and lowering glucose synthesis in the liver^[73].

G-protein coupled receptor 119

Muscles, liver, and pancreatic beta cells all contain G-protein coupled receptor 119 (GPR119). Like incretin hormones, the activation of GPR119 may increase insulin production and favor insulin secretion when agonists are attached to its binding site^[74]. GPR119 improves glucose homeostasis through two distinct mechanisms: The release of GLP-1 and GIP from enteroendocrine cells and the direct impact of the glucose-activated insulin release in β -cells^[75].

Glucose-dependent insulintropic polypeptide

One of the incretin hormones, or GIP, is found in the brain, fatty tissue, and β -cells. It enhances the insulin response prompted by the post-prandial rise in glycemia, where it plays a significant part in T2D and other metabolic disorders^[76]. By binding to the GIP receptor, GIP exerts its insulintropic effects by raising intracellular (cAMP) levels. PKA & exchange protein-activated cAMP2 are activated by elevated cAMP (EPAC2)^[77]. The depolarization of the voltage-gated Ca^{2+} channels increase the concentration of Ca^{2+} within the cell, which in turn initiates the release of Ca^{2+} from intracellular stores

through PKA and EPAC2. The elevation in Ca^{2+} concentration stimulates the transcription of the pro-insulin gene, which, in turn, contributes to an increase in the amount of insulin secreted by β -cells^[78].

5

Free fatty acid receptor 1

Free fatty acid receptor 1 (FFA1), also known as GPR-40, is a free fatty receptor. FFA1 is primarily present in pancreatic and intestinal cells. Researchers found that the FFA1 receptor affects lipid and glucose metabolism and boosts insulin release from pancreatic β -cells *in vivo* studies using mouse islets' β -cell lines. FFA1 impacts blood glucose levels by indirectly stimulating insulin release from pancreatic cells and increasing incretin hormones directly^[79].

FUTURE GOALS FOR DM

Gene therapy

Although very little knowledge exists about these targets' roles in diabetes, they can be critical in managing the disease. A new technique for treating DM is gene therapy, which works by repairing or correcting the defective genes that cause the disease^[80]. This approach allows for the replacement of the insulin gene and the transfer of genes *via* viral vectors and non-viral transduction methods to suppress auto-reactive T cells and prevent the destruction of islet cells. According to research, stem cells can be used to treat diabetes because they can readily multiply in culture and act as surrogate β -cells.

Additionally, research has discovered that rodents receiving intrahepatic injections of modified stem cells have low blood glucose levels (Table 2)^[81]. Under a fluorescent microscope, the stem cells fluoresce green after the mice have been slaughtered for histopathological examinations. Insulin was found using an anti-human insulin polyclonal antibody to stain the tissue^[32]. Mesenchymal stem cells successfully expressed human insulin and maintained blood glucose levels normal, according to a 42-d study. Compared to rodents that were not treated with gene therapy. As a result,

as a developing novel technology, genetic treatment has the potential to be used to treat DM^[82].

6 Leukocyte antigen-related tyrosine phosphatase & protein tyrosine phosphatase 1B

Leukocyte antigen-related tyrosine phosphatase and protein tyrosine phosphatase 1B (PTP1B) are critical players in the regulation of insulin signal transductions. An essential stage in the insulin signaling process is tyrosine phosphorylation in the insulin-receptor activation loop^[59]. Insulin signaling is negatively regulated by PTP1B, which dephosphorylates phosphor-tyrosine residues in insulin receptor kinase activation regions. More evidence shows that PTP1B, insulin sensitivity, obesity, and T2DM are all linked. PTP1B is also an essential part of the growth of β -cells in the pancreas^[83]. For example, Teimouri *et al*^[84] reported that PTP1B knockout mice have more cells, and more insulin is released when glucose is present. There is a lot of evidence from these studies that PTP1B plays a role in diabetes. This has sparked much interest in PTP1B inhibitors and the developing and discovery of several PTP1B inhibitors. There are other places where you can find more information about the reported PTP1B inhibitors.

11 beta-hydroxysteroid dehydrogenase

Cortisone, a glucocorticoid, is converted to cortisol, a hormone, by hydroxysteroid dehydrogenase. There are two isoforms of it presently available: 11 beta-hydroxysteroid dehydrogenase 1 (11 β -HSD1) and 11 β -HSD2. According to research, high blood amounts of glucocorticoids may lead to glucose intolerance, so maintaining 11 β -HSD1 levels naturally improves insulin sensitivity^[60]. According to one study, inhibiting the 11 β -HSD1 may improve insulin sensitivity by reducing insulin resistance and controlling the insulin signaling transduction system. When all the information listed above is considered, 11 β -HSD1 emerges as a new molecular target for DM treatment (Table 2)^[85].

Fetuin-A

A glycoprotein called fetuin-A is made in the liver and released into the bloodstream. The main protein needed to transport FFA to the bloodstream is fetuin-A. It also plays a role in-cell irritation and degeneration in the pancreas. Tyrosine kinase is a crucial enzyme for insulin signaling that thoroughly opposes insulin activity and is inhibited by fetuin-A (Table 2)^[86]. Tyrosine kinase and insulin work together to maintain a healthy blood sugar level. If the blood's fetuin-A content rises, it may lead to insulin resistance and eventually diabetes. Studies have shown that rodents with fetuin-A knockout genes have increased insulin sensitivity, demonstrating the negative relationship between fetuin-A and insulin sensitivity in diabetes^[87].

Serpin A12 or vaspin

Serpin A12, also known as vaspin, is a glycoprotein in serum that belongs to the superfamily "serpin". It is derived from fatty cells and significantly impacts insulin activity. It has been discovered that as the severity of diabetes rises, the serum levels of vaspin begin to fall. This raises the possibility that increasing the vaspin levels in circulation could aid in managing DM^[88]. Vaspin administration in rodents has been linked in studies on rodents to enhanced glucose tolerance and insulin sensitivity. This implies that it might be an option for therapy for managing metabolic disorders such as T2D and obesity. Vaspin can exert its effect by suppressing the insulin-degrading enzyme known as kallikrein 7 (KLK7), which in turn reduces the insulin's half-life and causes the insulin to be degraded more quickly (Table 2)^[89]. Because KLK7 is blocked, insulin signals work better, and insulin's half-life is lengthened, which helps lower blood glucose levels. It also does a few other things that indirectly reduce blood sugar. For example, it makes you eat less, which lowers your hepatic glucose production *via* increasing insulin signaling in the liver and reducing hepatic lipid accumulation^[90]. It decreases inflammation and boosts insulin signaling in brown adipose tissue and white adipose tissue. It activates the vagus nerve in the central nervous system to reduce appetite^[91].

Metnl

Metnl is an adipokine derived from the fatty tissues prevalent in the body's subcutaneous white fat. Metnl is crucial for sustaining immunological inflammation, cardiovascular function, lipid metabolism, energy metabolism, insulin sensitivity, and its essential role in maintaining glucose homeostasis (Table 2)^[92]. According to a report, researchers discovered that it functions by upregulating the PPAR pathway, which increases insulin sensitivity in mice models. Additionally, it has been found to encourage the browning of adipose tissue, increasing energy expenditure and better glucose tolerance^[93].

GPER

GPER is an orphan 7-transmembrane G-protein-coupled estrogen receptor that helps send signals about estrogen. They are found in the intracellular membranes of cells. Gi/o and Gs protein binding in organisms are crucial for controlling glucose homeostasis^[94]. It was discovered that a GPER-deficient female mouse model produces insufficient insulin, leading to DM. A study also found that estrogen levels are high in premenopausal women, which benefits glucose homeostasis, lipid metabolism, and blood pressure^[95]. In addition to decreasing inflammation, estrogen levels decline after menopause, making the female population more susceptible to metabolic disorders and insulin resistance, contributing to DM^[96]. This data suggests that GPER may be essential for managing diabetes and a valuable drug target for treating diabetes and associated disorders (Table 2).

Cellular communication network 3/nephroblastoma overexpressed

Cellular communication network 3 (CCN3), known as nephroblastoma overexpressed, is a protein high in cysteine with growth-regulating properties. Numerous human organs and bodily fluids, including the musculoskeletal system, kidneys, and cerebrospinal fluid, have been found to contain them^[59]. Hyperlipidemic obese patients

have substantially higher than expected plasma levels of CCN3, correlated with high-sensitivity C-reactive protein, body mass index, and fat mass. Dalle *et al*^[97] showed that mice who didn't have enough CCN3 and ate standard high-fat diets lost much weight and had better glucose tolerance and insulin sensitivity (Table 2). Furthermore, Li *et al*^[98] compared serum CCN3 levels in recently diagnosed T2DM (nT2DM) patients to healthy control subjects. CCN3 levels were significantly higher in T2DM individuals.

PEDF

The serine protease inhibitor family includes the 50 kDa PEDF, secreted from adipose tissue and the pigment cells of the human eye. It induces the insulin receptor substrate to undergo kinase-mediated serine/threonine phosphorylation, which results in decreased insulin signaling and insulin resistance in body cells (Table 2)^[99]. Additionally, the body's insulin sensitivity causes the production of interleukin-1 and tumor necrosis factor-alpha (TNF- α) in the system. The research discovered that animals' insulin sensitivity decreased after receiving PEDF but returned to normal after receiving anti-PEDF. PEDF correlates well with insulin resistance in infants and adults^[100]. Therefore, if we can lower the amount of PEDF in the blood, it might help the body respond better to insulin. This makes PEDF a possible new way to treat DM and other metabolic syndromes^[81].

Visfatin

Visfatin is a protein with many different functions. It is also called nicotinamide phosphoribosyl-transferase. It was founded in 2005. It can be found in several organs and tissues, but most comprise visceral adipose tissue. It has insulin-like properties, which means it helps to restore insulin sensitivity. This suggests that it may also play a role in diabetes, making it a new way to treat DM^[101]. It has been demonstrated that serum visfatin concentrations rise alongside the progression of T2DM, establishing a relationship between visfatin and T2DM. Current research has shown that visfatin binds to the insulin receptor at a location different from that of insulin, suggesting that

it has properties similar to insulin and stimulates cell growth^[102]. Though scientists are investigating the underlying mechanisms of visfatin in DM, it is unclear how visfatin is fully linked to the disease. Nevertheless, there are some visfatin stimulators and inhibitors. With this knowledge, it is possible to conclude that visfatin and diabetes are related in the body, making it an appropriate focus for DM treatment (Table 2)^[103].

ACRP 30

ACRP 30 or Adipocyte complement protein of 30 kDa, the capacity of adipose tissue to store fat has long been known. However, current studies have demonstrated that it may serve as a reservoir of hormones such as Acrp30, adiponectin, resistin, TNF- α , leptin, or adipsin^[104]. TNF- α is a crucial pro-inflammatory mediator responsible for insulin resistance, and serum protein Acrp30 is found to serve a primary part in managing DM. In addition, another report reveals that Acrp30 levels are reduced in numerous obesity and diabetes models^[105]. Since mice missing Acrp30 exhibit insulin resistance, which results in the development of DM, high TNF- α levels also demonstrate a negative correlation of this protein with DM (Table 2)^[106]. When the concentration of Acrp30 in the blood is raised, insulin sensitivity can also be elevated, making it easier to control blood glucose levels. As a result, Acrp30 will potentially become an additional avenue for the therapy of DM^[107].

IMPACT OF SOCIAL DETERMINANTS ON DM

Current literature increasingly underscores the substantial influence of social determinants on the development, management, and outcomes of DM. This section aims to provide an updated perspective on this critical aspect, incorporating recent research findings and insights. Recently, studies have reaffirmed the strong association between socioeconomic status (SES) and the prevalence of diabetes. A study by Liu *et al*^[108] highlighted a significant correlation between lower SES and a higher risk of developing diabetes. This socioeconomic gradient in diabetes incidence has been consistently observed in diverse populations.

Data from Tapager *et al*^[109] emphasize the role of healthcare access in diabetes management. Their findings indicate that individuals with limited access to healthcare services face more significant challenges in managing their diabetes, resulting in health disparities. This observation aligns with the growing awareness of differences in diabetes outcomes based on factors such as race and geography. Moreover, research published by Kanchi *et al*^[110] has shed light on the significance of the food environment in diabetes risk. Their study demonstrated that neighborhoods with limited access to fresh and healthy food options were associated with higher rates of diabetes incidence. This highlights the importance of addressing the food environment as a key social determinant in diabetes prevention and management.

The latest research on psychosocial factors and how they affect diabetes control has revealed significant new information. According to a study by Abate and Gedamu^[111], stress and social support networks significantly impact how well people with diabetes manage their blood sugar levels. These results highlight the importance of comprehensive psychosocial support in treating diabetes. Based on these recent findings, our discussion aims to underscore the evolving understanding of how social determinants intricately shape the landscape of DM. These insights emphasize the need for a multifaceted approach that considers clinical factors and the social, economic, and environmental contexts in which diabetes occurs.

CONCLUSION

DM is a pervasive and challenging health condition affecting a substantial population worldwide. The primary goal of DM therapies is to achieve near-normal blood glucose levels. However, it is essential to acknowledge that current treatments cannot offer a complete cure; they can only manage symptoms and slow the progression of the disease, often accompanied by a range of adverse effects. The quest for innovative solutions to address DM and its consequences is an ongoing endeavor within the scientific community. Researchers are steadfast in their pursuit of compounds that could potentially offer a lasting remedy for DM with minimal side effects. While

traditional methods, such as insulin therapy and biguanides, have been relied upon for an extended period, other classes of medications, including sulphonylureas, glinides, thiazolidinediones, gliptins, inhibitors of α -glucosidase, analogs of amylin, SGLT-2 inhibitors, and dopamine D-2 agonists, have also been explored. Unfortunately, these treatments are not without limitations, often presenting adverse effects ranging from bladder cancer to hypoglycemia and weight gain.

In response to these challenges, researchers have been actively investigating alternative targets for diabetic therapy. While targets like PPARs have garnered significant attention over the past decade, the translation from pre-clinical research to clinical studies and commercialization has been limited. This underscores the pressing need for novel, creative pharmacological targets in diabetes management. In light of recent advancements, several receptors, including GPCR 119, GPER, GPCR, GIP, MLT, visfatin, ACRP 30, fetuin-A, PEDF, metnl, vaspin, and 11-hydroxysteroid dehydrogenase-1, have emerged as promising candidates that play a direct or indirect role in insulin regulation. These receptors hold the potential to be leveraged as therapeutic targets for diabetes management, paving the way for the development of long-term remedies and the mitigation of its complications. Furthermore, it is worth noting that cutting-edge approaches, such as gene therapy and stem cell-based interventions, hold the promise of delivering treatments with increased efficacy and fewer adverse effects. These innovative strategies represent exciting avenues for exploration in the pursuit of more effective and patient-friendly interventions for DM.

In conclusion, while we acknowledge the challenges associated with the existing approaches to diabetes management, we remain optimistic about the future of diabetes research and therapy. Our understanding of the intricacies of this condition continues to evolve, offering fresh perspectives and novel opportunities. We encourage continued exploration into the receptors and innovative therapies discussed here, anticipating that they will contribute significantly to developing effective, enduring solutions for DM and its associated complications.

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