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**Analysis of the management and therapeutic performance of diabetes mellitus using special targets**

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

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**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 the tissue-acting effects of insulin, 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 might rise to 430 million in the coming years. The major factors in deterioration of DM include age, obesity, and sedentary lifestyle. Finding new therapies to manage DM safely and effectively without jeopardizing patient compliance has always been essential. Among the medications available to manage DM are glucagon-like peptide-1 agonists, thiazolidinediones, sulphonyl urease, glinides, biguanides, and insulin-targeting receptors discovered > 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 used as targets in treating DM 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 by hyperglycemia. Major contributing factors are insufficient insulin secretion, insulin resistance, or both. Global diabetes prevalence has risen from 4% to 6.4% in the past 30 years and may reach 430 million in the future. Age, obesity and a sedentary lifestyle exacerbate the disease. Developing safe and effective therapies is crucial. Medications like glucagon-like peptide-1 agonists, thiazolidinediones, and others have been available for over a decade. However, clinical observations suggest ongoing research. This review focuses on insulin regulation targets for potentially more efficient and secure diabetes treatments.

**INTRODUCTION**

Diabetes mellitus (DM) is one of the most common conditions, and is presently the seventh leading cause of death, with 5.2 million worldwide[1]. DM that is 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 (8.5%) in 2017, it is expected that 629 million people will have DM by 2045. The cost of treating DM 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 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 DM[4]. DM 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].

DM is classified into three types: type 1 (T1DM), type 2 (T2DM), gestational DM (GDM), and other variants. T1DM affects 5%–10% of individuals diagnosed with it, usually young children and teenagers[6]. A complete lack of insulin production brings on T1DM. T2DM, which is more common, is caused by inadequate corrective insulin secretory response and resistance to insulin action[7]. Around 90%–95% of people with DM have T2DM, which continues to increase worldwide[8]. In the 20 years following delivery, GDM increases the chance of T2DM by 35%–60%. One in every six live births is complicated by GDM, which occurs in the second or third trimester of pregnancy[8]. Drug-induced DM, pancreatic illness, and monogenic DM are additional types. Type 1.5 DM, 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 DM typically causes unintentional weight loss, increased excretion, increased thirst, and increased appetite[10]. T1DM symptoms can appear suddenly, whereas T2DM symptoms typically appear more gradually and may even be nonexistent. About half of the people do not realize they have T2DM because there are few symptoms or signs in the early stages of the disease. As a result, symptoms go undetected and lead to diabetic complications[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].

DM 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 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 DM management[12]. This review aims to analyze the management and treatment 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 antidiabetic drugs.

**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 synthesis of glucose in the liver through glycogenolysis and gluconeogenesis[13] or by boosting glucose uptake by the liver, muscle, and fat tissues, 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 or 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 insulinotropic polypeptide, glucagon-like peptide-1 (GLP-1), and amylin are additional hormones that help to maintain an average blood glucose level [glucose-dependent insulinotropic 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 cotransporter (SGLT) and facilitative glucose transporter are two examples of the two kinds of glucose transporters, which are a family of membrane-bound glycoproteins[20]. The interplay of genetic and environmental factors largely determines T2DM. The risks increase with increasing levels of overweight or obesity. Hormonal changes that arise during pregnancy are the cause of GDM. 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 DM or maturity-onset DM of young people are DM at birth and DM 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 beta cells or decrease their ability to produce insulin. Diabetes develops if the damaged pancreas is removed due to beta-cell loss[24] (Figure 1).

**MANAGEMENT OF DM**

Management of DM aims to boost output and quality of life by: (1) early detection; (2) long-term and short-term morbidity prevention; (3) early death prevention [25]; (4) supporting patients’ freedom and self-care habits; and (5) reduction of the personal, family, and societal burden. Achieving these objectives depends on the facilities and health care team being successfully established. This involves educating those with DM and healthcare professionals[26].

***Blood sugar level***

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 DM is for each patient to keep track of their blood glucose levels and how exercise and food affect them. Patients can improve their DM management by changing their habits[28].

***Hypo- and hyperglycemia***

A hypoglycemic episode is a glucose level of 3.8 mmol/L, and 55% of cases of severe hypoglycemia occur during sleep in T1DM that is well-controlled. Six percent of fatalities in people with DM aged < 40 years are attributed to nocturnal hypoglycemia (dead-in-bed syndrome)[29]. According to the National Institute of Health data, hypoglycemia accounts for 2%–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 neuropathy, hypoglycemia can also start or exacerbate neuropathy in people with DM 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***

Glycemic control refers to the typical blood sugar levels of a person with DM. A lot of evidence indicates that years of hyperglycemia cause multiple serious issues of diabetes, especially complications of microvascular origin. Effective glycemic control, in the sense of a target for treatment, has become a crucial aim of DM care despite recent research suggesting that genetic factors may be accountable for diabetic complications[32]. T1DM 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 glycemic control in research studies and clinical therapy for people with DM[33].

The HbA1c test measures the average glucose levels over the prior 2 or 3 mo. By the most popular measures, HbA1c is typically 4%–6% in nondiabetic 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 glycemic control[34]. There has been no difference in all-cause mortality, nonfatal stroke, or limb amputation in extensive studies comparing the impact of strict glycemic control to conventional or more relaxed glycemic control in T2DM. 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 monitoring by patients, especially those with T1DM, may improve management and outcomes for both T1DM and T2DM. Keeping track of 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 T1DM, self-testing is crucial because insulin therapy can result in low blood sugar (hypoglycemia), and home testing allows patients to adjust the dose each time they administer insulin. A new study suggests that self-monitoring does not improve blood glucose control or quality of life, even though its efficacy in T2DM has been more controversial. Despite home blood glucose monitoring, T2DM patients are considered to have poor long-term management[38].

Continuous glucose monitoring technology has improved to provide data regarding the pace and pattern of glucose changes in people with DM. 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 continuous glucose monitoring 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].

***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 3 mo, has been suggested to emphasize the most recent 2–4 wk[41]. HbA1c levels range from 4.0 to 6.0 in people who do not have DM. People with DM whose HbA1c levels stay < 6.5% are said to have reasonable glycemic control[37]. If diet or treatment adjustments have been made within the last 6 wk, 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 2–3 wk[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 100 000 health-related apps are available on Google Play and the App Store, and the most general category is DM 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].

A 2016 study of 65 Android DM 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 T2DM Android mobile app 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] examined the effectiveness and applicability of digital tools designed to assist women with GDM dietary self-management.

***Foot examination***

The likelihood of diabetic foot ulcers can be predicted by keeping an eye on patients’ 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 T1DM[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 diabetic cardiomyopathy[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 T2DM 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 T1DM 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 T1DM more susceptible to nocturnal hypoglycemic episodes[52]. Although exercise may not directly lower blood glucose levels in with T1DM, 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 DM work 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. There are several distinct types of antidiabetic medications[54]. A basal-bolus regimen that most closely mimics natural insulin release is optimal for treating T1DM: long-acting insulin for the basal rate and short-acting insulin with food[55]. Most people with T2DM are treated with oral medication, although some ultimately need to be treated intravenously with insulin or GLP-1 agonists. Metformin is usually recommended as the initial therapy for T2DM 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 FOR DM USING SPECIAL TARGETS**

Even though biomedicine has made a lot of progress and we are learning more about how to treat different diseases, DM is still hard to treat. To solve this problem, researchers from various fields are looking for a way to treat DM 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]. Antidiabetic drugs like dipeptidyl peptidase 4, thiazolidinedione, sulfonylurea, or metformin inhibitors are currently used to treat DM. However, these drugs cannot entirely limit DM, 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 DM: thiazolidinediones, gliptins, GLP-1, glinides, biguanides, insulin, peroxisome proliferator-activated receptor (PPAR) agonists, sulphonylureas, β-glucosidase inhibitors, amylin mimics, SGLT-2, and dopamine D2 agonists[60]. Pro-hormone convertases (PC I 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, METRNL, 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 T2DM 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].

PPAR agonists, especially PPAR-γ agonists like pioglitazone, regulate glucose and lipid metabolism and increase insulin sensitivity in peripheral tissues. DM patients treated with PPAR-γ 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 PPAR agonists. Several investigations have indicated changes in vaspin levels in individuals with DM. 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 DM. 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**

Traditional diabetic drugs are well-known treatment options that have been available in the market for a long time. Still, their availability is restricted, and they come with several drawbacks, such as weight gain and hypoglycemia. 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 renal excretion of glucose. α-Glucosidase inhibitors reduce intestinal uptake of glucose and free fatty acids (FFAs). Pancreatic insulin production and sensitivity are both improved by sulphonyl urease. The release of FFAs 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 T2DM because it also regulates glucose and the pancreatic release of insulin. It exerts its pharmacological effects by interacting with the MT1 and MT2 receptors[70]. Recent research has revealed that mice lacking the MT1 receptor exhibit increased insulin resistance and glucose intolerance. The MT1 receptor is an important therapeutic target for controlling blood sugar levels[71].

***PPARs***

PPARs are transcription factors that control gene expression, of which there are three types: PPARα, PPARγ and PPARβ/δ[72]. Thiazolidinediones and PPAR agonists activate PPARs, making the body more sensitive to insulin. After activation, they lower the levels of FFAs 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].

***GPR119***

Muscles, liver, and pancreatic beta cells all contain 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 beta cells[75].

***GIP***

One of the incretin hormones, GIP, is found in the brain, fatty tissue, and beta cells. It enhances the insulin response prompted by the postprandial rise in glycemia, where it plays a significant part in T2DM and other metabolic disorders[76]. By binding to the GIP receptor, GIP exerts its insulinotropic effects by raising intracellular cAMP levels. Protein kinase A and exchange-protein-activated cAMP2 (EPAC2) are activated by elevated cAMP[77]. The depolarization of the voltage-gated Ca2+ channels increases the concentration of Ca2+ within the cell, which in turn initiates the release of Ca2+ from intracellular stores through protein kinase A and EPAC2. The elevation in Ca2+ concentration stimulates the transcription of the pro-insulin gene, which, in turn, contributes to an increase in the amount of insulin secreted by beta cells[78].

***FFA receptor 1***

FFA receptor 1 (FFA1), also known as GPR-40, an FFA receptor. FFA1 is primarily present in pancreatic and intestinal cells. Researchers have found that FFA1 affects lipid and glucose metabolism and boosts insulin release from pancreatic beta cells *in vivo*, using beta cells from mouse islets. 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 there is little knowledge about the role of these targets in DM, 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 autoreactive T cells and prevent the destruction of islet cells. According to research, stem cells can be used to treat DM because they can readily multiply in culture and act as surrogate beta 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].

***Leukocyte antigen-related tyrosine phosphatase and 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 beta 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.

***11β-Hydroxysteroid dehydrogenase***

Cortisone, a glucocorticoid, is converted to cortisol, a hormone, by hydroxysteroid dehydrogenase. There are two isoforms of it presently available: 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) and 11β-HSD2. According to research, high blood amounts of glucocorticoids may lead to glucose intolerance, so maintaining 11β-HSD1 levels naturally improves insulin sensitivity[60]. According to one study, inhibiting the 11β-HSD1 may improve insulin sensitivity by reducing insulin resistance and controlling the insulin signaling transduction system. When all the information listed above is considered, 11β-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 FFAs 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 fetuin-A level in the blood rises, it may lead to insulin resistance and eventually DM. 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 DM increases, 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 T2DM and obesity. Vaspin can exert its effect by suppressing the insulin-degrading enzyme known as kallikrein 7 (KLK7), which in turn reduces the half-life of insulin and causes insulin to be degraded more quickly (Table 2)[89]. Because KLK7 is blocked, insulin signals work better, and the half-life of insulin 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].

***METRNL***

METRNL is an adipokine derived from the fatty tissues prevalent in subcutaneous white fat. METRNL 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]. Researchers have discovered that it functions by upregulating the PPAR pathway, which increases insulin sensitivity in mouse 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 suggests that GPER may be essential for managing DM and a valuable drug target for treating diabetes and associated disorders (Table 2).

***Cellular communication network 3/nephroblastoma overexpressed***

Cellular communication network 3 (CCN3), also 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 that did not have enough CCN3 and ate standard high-fat diets lost a lot of weight and had better glucose tolerance and insulin sensitivity (Table 2). Li *et al*[98] compared serum CCN3 levels in recently diagnosed T2DM patients and 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-α (TNF-α) in the system. Insulin sensitivity in animals 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 discovered 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 DM, making it a new way to treat the disease[101]. It has been demonstrated that serum visfatin concentrations rise alongside the progression of 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]. Although 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, also known as adipocyte complement protein of 30 kDa, has been identified for its ability in adipose tissue to store fat for an extended period of time. 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 proinflammatory mediator responsible for insulin resistance, and serum protein Acrp30 is found to serve a primary part in managing DM. Another study revealed that Acrp30 levels were reduced in numerous obesity and DM models[105]. Mice missing Acrp30 exhibit insulin resistance, which results in the development of DM, and 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 and the prevalence of DM. A study by Liu *et al*[108] highlighted a significant correlation between lower socioeconomic status and a higher risk of developing DM. This socioeconomic gradient in DM incidence has been consistently observed in diverse populations.

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

The latest research on psychosocial factors and how they affect DM control has revealed significant new information. According to a study by Abate and Gedamu[111], stress and social support networks significantly affect how well people with DM manage their blood sugar levels. These results highlight the importance of comprehensive psychosocial support in treating DM. 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 therapy 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, amylin analogs, SGLT-2 inhibitors, and dopamine D2 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 therapeutic targets for DM. While targets like PPARs have garnered significant attention over the past decade, the translation from preclinical research to clinical studies and commercialization has been limited. This underscores the pressing need for novel, creative pharmacological targets in DM management. In light of recent advancements, several receptors, including GPCR119, GPER, GPCR, GIP, MLT, visfatin, ACRP 30, fetuin-A, PEDF, METRNL, vaspin, and 11β-HSD1, 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 DM, paving the way for the development of long-term remedies and the mitigation of its complications. 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 DM management, we remain optimistic about the future of 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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**Figure Legends**



**Figure 1 Illustration of the pathophysiology of type 1 and 2 diabetes mellitus.** DM: Diabetes mellitus.

**Table 1 Antidiabetic medications authorized by the** **US Food and Drug Administration**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of agents** | **Dosing** | **Formulation** | **FDA clearance date** | **Observations** |
| Euglycemics: Drugs that lower blood sugar levels to typical levels. These drugs should not result in higher blood glucose levels. |
| Biguanides: Reduce intestinal glucose absorption and hepatic glucose release and enhances insulin sensitivity (increases glucose uptake and utilization) |
| Metformin: Glumetza Fortamet®, Glucophage XR®, Glucophage® | 500 mg, 1000 mg. 500 mg, 750 mg pills. 500 mg, 750 mg pills. 500 mg, 850 mg, and 1000 mg pills | Initial dose: 500 mg once daily. Dose: 2 or 3 times daily. Range: 500-2550 mg. Initial: 500 mg 2 times daily or 850 mg once a day | December 1994 | SE: Cannot use if patients have problems with liver or kidneys; take drugs for heart failure; or drink too much alcohol. Consume with food (ER with evening meal) 0.03 cases per 1000 individuals have lactic acidosis. Gastrointestinal complaints (3%) such as diarrhea, nausea, and upset stomach |
| Thiazolidinediones, also known as glitazones or TZDs, are compounds that lower insulin intolerance (muscle and fat tissues) |
| Rosiglitazone: Avandia® | Tablets of 2 mg (pink), 4 mg (orange), and 8 mg (red–brown) | Initially: 4 mg per day. Range: 4-8 mg. Take it once or twice every day | May 1999 | SE: Bone loss and fractures in women, anemia, edema from fluid retention, weight increase, macular edema (in the eye), and may raise the chance of heart issues, such as angina or heart attacks, may lead to or exacerbate cardiac failure. Patients cannot use this with severe heart failure or liver disease. Liver surveillance is necessary |
| Pioglitazone (preferred over rosiglitazone): Actos® | Tablets, 15 mg, 30 mg, and 45 mg (white to off-white) | 15-30 mg initially; 15-45 mg daily. Dose: One dose per day | July 1999 | SE: Bone loss and fractures in women, anemia, edema from fluid retention, weight increase, macular edema (in the eye), and may lead to or exacerbate cardiac failure. Patients cannot use this with severe heart failure or liver disease. Liver surveillance is necessary |
| GLP-1 analogs: Make more insulin, stop the liver from releasing glucose after meals, keep the stomach from emptying as quickly, and make people feel full |
| Dulaglutide: Trulicity® | 1.5 mg or 0.75 mg each time. Under the epidermis (subcutaneous), injection available in single-dose, dose-specific pen instruments | At first: 0.75 mg once per week. Range: If the reaction is insufficient, it may be increased to 1.5 mg once weekly | September 2014 | SE: Sickness, diarrhea, vomiting, stomach pain. Cannot be used if patients have multiple endocrine neoplasia syndrome type 2, or a family history of medullary thyroid cancer (MEN2). In patients with a history of medullary thyroid cancer, it is contraindicated; there have been a few cases of pancreatitis (inflammation of the pancreas) |
| Albiglutide: Tanzeum® | 30 mg or 50 mg each time under the epidermis (subcutaneous), Administration of 30 mg or 50 mg doses via subcutaneous (SQ) injection is facilitated using single-dose pens designed for convenient and accurate dosing.paticular  | Initial: 30 mg once weekly. Range: Can increase to 50 mg once weekly if inadequate response | September 2014 | SE: Upper respiratory infection, nausea, and injection site response. Infrequent cases of pancreatitis (inflammation of the pancreas); contraindicated in patients with a history of medullary thyroid cancer |
| SGLT2 inhibitors: Make people excrete more glucose in the urine |
| Dapagliflozin: Farxiga® | 5 mg tablets are yellow and round, and 10 mg tablets are yellow and diamond-shaped | 5 mg once every day at first. Up to 10 mg per day | January 2014 | SE: Increased urination, UTIs, genital yeast infections, dizziness, lower blood pressure, increase in blood potassium; rare severe allergic reactions (severe rash; swelling of the pharynx tongue, body or face) (swelling of the tongue, throat, face or body; severe inflammation). If patients have kidney disease, they cannot use this product |
| Empagliflozin: Jardiance® | Tablets 10 mg (pale, beige, round) and 25 mg (pale, beige rectangular) | Initial: 10 mg once daily. Range: Up to 25 mg daily | August 2014 | SE: Rare severe allergic responses, frequent urination, low blood pressure, dizziness, genital yeast infections, and urinary tract infections; and a rise in blood potassium (swelling of tongue, throat, face, or body; severe rash). Do not take it if patients have renal disease |
| Canagliflozin: Invokana® | Tablets come in two different dosages and pill colors: 100 mg (colored yellow) and 300 mg (colored white) | At first: 100 mg every day. Range: 100-300 mg per day. Dose: One dose per day | March 2013 | SE: frequent or urgent urination, low blood pressure, dizziness, genital yeast infections, UTIs, a rise in blood potassium, and severe but uncommon allergic reactions (swelling of the tongue, throat, face, or body, severe rash). Do not take it if patients have renal disease |
| DPP-4 inhibitors: Increased insulin production and decreased postprandial liver glucose release are two effects |
| Linagliptin: Tradjenta® | 5 mg (red-light) tablet | At first, 5 mg every day. Dose: One dose per day | May 2011 | SE: No weight gain, nasal congestion, throat pain, rare reports of pancreatitis, extremely rare severe allergic reactions |
| Saxagliptin: Onglyza® | 2.5 mg tablets are pale to light yellow, and 5 mg tablets are pink | Range: 2.5-5 mg daily, starting with 2.5 or 5 mg. Dose: One dose per day | July 2009 | SE: Headache, urinary tract illness, and upper respiratory infection. No weight gain. If kidney issues exist, lower amounts are used |
| Sitagliptin: Januvia® | Tablets of 25 mg (pink), 50 mg (light brown), and 100 mg (beige) | At first, take 100 mg every day. Daily dose: 25-100 mg. Dosage: Once every day | December 2006 | SE: runny nose, upper respiratory infection, and uncommon severe allergic responses (swelling of the tongue, throat, face, or body, severe rash). No weight increase. If there are kidney issues, lower doses are used |
| Alogliptin: Nesina® | Tablets of 6.25 mg (light pink), 12.5 mg (yellow), and 25 mg (light red) | Every day, take 25 mg by mouth. Given once a day | January 2013 | SE: Upper respiratory infection, headache, sore throat, stuffy or runny nose, uncommon serious allergic responses (swelling of the tongue, throat, face, or body), and severe rash. Accounts of pancreatitis are uncommon. No weight increase |
| α-Glucosidase inhibitors: starch blockers are substances that slow down the digestive process and the assimilation of carbohydrates |
| Acarbose: Precose® various generics | Tablets of 25 mg, 50 mg, and 100 mg | Initial: Three times per day, 25 mg, 75 to 300 mg. Maximum 150 mg if under 60 kg. Dose: Three times per day | September 1995 | SE: Defecation. Take with the first mouthful of food. To avoid GI intolerance, begin with a modest dose and gradually increase it |
| Stimulators of insulin release (insulin secretagogues): Raise the amount of insulin the liver produces |
| Glinides |  |  |  |  |
| Nateglinide: Starlix® | Tablets of 60 mg (pink) and 120 mg (yellow) | 120 mg three times every day at first (if A1C is close to goal, use 60 mg). Range: 180-360 mg daily dosage is three times | December 2000 | SE: Syndrome of uncontrolled hypoglycemia protection for older patients. Only 2 h of physical activity or exercise is involved. Take it within 30 min of eating |
| Repaglinide: Prandin® | Tablets of 0.5 mg (white), 1 mg (yellow), and 2 mg (red) | Starting dose: 1-2 mg daily (0.5 mg if A1C 8%). From 0.5 to 16 mg. The maximum dose is 4 mg per dinner. Given twice, three times, or four times per day | December 1997 | SE: Hypoglycemic. It is safe for older adults. The activity lasts only 4 h. Take 15-30 min after eating |
| SFUs |
| Glimepiride: Amaryl® various generics | Tablets ranging from 1 mg to 4 mg | To start, try 1-2 mg once a day. Between 1 and 8 mg. One daily dose is recommended | November 1995 | SE: Weight increase and hypoglycemia. Only one daily dose is necessary |
| Glyburide, micronized: Glynase PresTab® various generics | Tablets with dosages of 1.5 mg, 3 mg, 4.5 mg, and 6 mg | Initial: 1.5-3 mg/d; permitted range: 0.75-12 mg. Dosage: One or two daily doses (if > 6 mg) | March 1992 | SE: Weight increase and hypoglycemia |
| Glyburide: Micronase®, DiaBeta® various generics | Tablets of 1.25 mg, 2.5 mg, and 5 mg | Initial: 2.5-5 mg everyday. Range: 1.25-20 mg. To be consumed once or twice every day | May 1984 | SE: Hypoglycemia and obesity  |
| Glipizide: Glucotrol®, Glucotrol XL® various generics | Tablets of 5 mg and 10 mg. Tablets of 2.5 mg, 5 mg, and 10 mg ER | At first, 5 mg every day. From 2.5 to 40 mg (20 mg for XL). Dosage: once or twice daily (if more than 15 mg) | May 1984. April 1994 | SE: Hypoglycemia and weight increase. SFU is preferred by older patients.  |
| Oral pills in combination |
| Empagliflozin/metformin, Synjardy® | 12.5 mg/500 mg (pale brownish purple), 12.5 mg/1000 mg (dark brownish purple), 5 mg/500 mg (orange-yellow), 5 mg/1000 mg (brownish yellow). Tablet with an oval sheet coating | Starting dose: 5 mg/500 mg or 5 mg/1000 mg. Maximum dose: 25 mg/2000 mg split into two doses | January 2015 | SE: Same as for empagliflozin and metformin |
| Empagliflozin/linagliptin, Glyxambi® | Triangular pills, 10 mg/5 mg (pale yellow), 25 mg/5 mg (pale pink) | At first: 10 mg/5 mg once every day. Range: 5 mg once every day up to 25 mg | February 2015 | SE: Same as for empagliflozin and linagliptin |
| Dapagliflozin/metformin XR, Xigduo XR® | 10 mg/500 mg (pink), 10 mg/1000 mg (pink to dark pink), and 5 mg/500 mg (orange) (yellow to dark yellow) oval tablets covered in celluloid | Starting dose: The patient’s present regimen up to 10 mg/2000 mg per day | October 2014 | SE: As previously mentioned |
| Canagliflozin/metformin, Invokamet® | Film-coated capsule-shaped pills, 50 mg/500 mg (white), 50 mg/1000 mg (beige), 150 mg/500 mg (yellow), and 150 mg/1000 mg (purple) | Beginning: With 50 mg/500 mg or 50 mg/1000 mg. Range: 300 mg to 2000 mg. Taken in 2 divided quantities | August 2014 | SE: Same as for metformin and canagliflozin |
| Alogliptin/pioglitazone, Oseni® | The next round of pills is available: 25 mg/45 mg (red), 25 mg/30 mg (peach), 25 mg/15 mg (yellow), 12.5 mg/15 mg (pale yellow), 12.5 mg/30 mg (pale peach), 12.5 mg/45 mg (pale red) | Initial dosage: Once daily, 12.5/15 mg. Range: 25/45 mg and higher ingested with or without food once daily | January 2013 | SE: Same as for pioglitazone and alogliptin |
| Alogliptin/metformin, Kazano® | Oblong pills, 12.5 mg/1000 mg (pale yellow), 12.5 mg/500 mg (pale yellow) | At first: 12.5 mg/500 mg once or twice every day. Maximum range: 25/2000 taken with meals twice a day | January 2013 | SE: Same as for alogliptin and metformin  |
| Linagliptin/metformin, Jentadueto® | Oval pills with dosages of 2.5 mg/1000 mg (light pink), 2.5 mg/850 mg (light orange), and 2.5 mg/500 mg (golden yellow) | Initial dosage: 2 times a day with food, 2.5 mg/500 mg. Range: Twice daily dosages of up to 2.5 mg/1000 mg food | January 2012 | SE: Same as for linagliptin and metformin |
| Sitagliptin/metformin, Janumet XR® | Oval pills, 50 mg/500 mg (light blue), 50 mg/1000 mg (light green), and 100 mg/1000 mg (blue) | At first: 100 mg/1000 mg every day. Maximum daily dose: 100 mg/2000 mg. Dosage: Once every day | February 2012 | SE: Same as for sitagliptin and metformin  |
| Saxagliptin/metformin XR, Kombiglyze XR® | Capsule-shaped pills contain 2.5 mg/1000 mg (pale yellow to light yellow), 5 mg/1000 mg (pink), and 5 mg/500 mg (golden brown to brown) | Starting dose: 5 mg/500 mg or 5 mg/1000 mg once daily. Maximum dose: 5 milligrammes/2000 mg. Dosage: Once every day | November 2010 | SE: Same as for metformin and saxagliptin |

SE: Side effects; SFUs: Sulfonylureas; TZD: Thiazolidinediones; GLP: Glucagon-like peptide; DDP: Dipeptidyl peptidase; UTI: Urinary tract infection; ER: Extended release; FDA: Food and Drug Administration.

**Table 2 Recently developed novel antidiabetic targets and their method of activities**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Nature** | **Special targets** | **Diabetics** | **Method of activity** | **Refs** |
| Gene | Gene therapy | Autoreactive T cells need to be stopped from killing islet cells | Act by fixing or modifying the problematic genes | [81] |
| Glycoprotein in serum | SERPIN A12 or vaspin | KLK7 reduction enhances insulin signaling and lengthens the half-life of insulin, contributing to lower blood sugar levels | Vaspin blocks KLK7 | [89] |
| Adipokine | Metrnl | Enhanced insulin responsiveness | Cause of PPAR pathway upregulation | [92] |
| Hormone | ACRP-30 | Acrp30 increases insulin sensitivity and lowers blood sugar | Low amounts bring on insulin sensitivity | [106] |
| Glucocorticoids | 11β-HSD1 | 11β-HSD inhibition glucose reduction, insulin sensitivity improvement | Increasing amounts lead to glucose sensitivity | [85] |
| Glycoprotein | Fetuin-A | When fetuin-A levels are low, insulin sensitivity will go up | Associated with beta-cell inflammation | [86] |
| Glycoprotein | GPER | Boost insulin production | Through binding with Gi/o and Gs proteins, glucose homeostasis is regulated | [94] |
| Glycoprotein | PEDF | Insulin sensitivity is improved by reducing PEDF levels | Insulin resistance is caused by an upregulated chain of kinase-mediated serine/threonine phosphorylation of IRS | [99] |
| Protein | Visfatin | Activity that mimics insulin | Receptor for insulin that it binds to | [103] |
| Protein | CCN3/NOV | Improved glucose tolerance and insulin sensitivity | Strong correlation with hs-CRP | [97] |
| Glycoprotein | PTP1B |  | Inhibits insulin signaling by dephosphorylating insulin receptor kinase | [83] |

KLK7: Kallikrein 7; PPAR: Peroxisome proliferator-activated receptor; 11β-HSD1: 11 beta-hydroxysteroid dehydrogenase 1; GPER: G protein-coupled estrogen receptor; PEDF: Pigment epithelium-derived factor; CCN3/NOV: Cellular communication network 3/nephroblastoma overexpressed; PTP1B: Protein tyrosine phosphatase 1B; hs-CRP: High-sensitivity C-reactive protein.



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