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DIABETES MELLITUS: SHIFT TOWARDS HERBAL TREATMENT

Prashant Kumar Bharti*[1], Nidhi Gupta[2], Jyoti Yadav[3] and Dheeraj Kumar[4]

[1,3,4]Department of Pharmacology, Institute of Technology Management Gida Gorakhpur.

[2]Department of Pharmacology, Institute of Technology of Pharmacy and Research Gida Gorakhpur.

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***Corresponding Author**
Prashant Kumar Bharti
Department of Pharmacology, Institute of Technology Management Gida Gorakhpur.
Prashantkumarbharti321@gmail.com

ABSTRACT

Over past three decades, prevalence of diabetes mellitus has quadrupled worldwide, making it the ninth most common cause of death. Today, 90% of people with diabetes have diabetes mellitus (DM), accounting for 1 in 11 cases worldwide. With China and India acting as the top two epicenters, Asia is a major hotspot for the global DM epidemic. Genetic predisposition plays a role in an individual's susceptibility to diabetes mellitus (DM), but poor diet and sedentary lifestyle are major contributors to the current global epidemic; prenatal exposures and other early developmental variables also play a role in an individual's later-life susceptibility to DM. Making healthy lifestyle changes can prevent many cases of diabetes mellitus. A growing number of individuals are predicted to live with diabetes mellitus, a complex chronic health illness that impacts a large percentage of people. Given that the vast majority of diabetic patients (about 90–95%) suffer from type 2 diabetes mellitus and that this study focuses on potential drugs that target many targets involved in treating type 2 diabetes, as mono-target treatment often fails to regulate blood glucose levels and other problems.

KEYWORDS: Diabetes mellitus, epidemic, blood glucose level, type 2 diabetes mellitus.

1. INTRODUCTION

Diabetes Mellitus (DM) is a chronic illness that is caused by a complex interplay of genetic and/or environmental factors.[1,2] It is true that this pathology is highly familiar, and different ethnic groups—such as Hispanic and Black people—have varying rates of diabetes. Minorities with a particular genetic profile, such as American Indians and Native Alaskans,

have a higher risk of developing diabetes. Number of adults with diabetes has nearly quadrupled to 422 million since 1980, according to the World Health Organization's (WHO) Global Report on Diabetes[3], expected to reach 693 million by year 2045.[4] Because insulin is insufficient, syndrome is characterized by consistently high blood glucose levels, pancreatic hormone responsible for controlling blood sugar, either in terms of concentration or activity.

Diabetes can be managed and treated, but there is currently no known cure. It may be necessary to use insulin and/or pharmaceutical therapy to prevent or delay development of diabetes-related complications by maintaining normal or near-normal blood glucose levels. Nonetheless, maintaining a healthy diet and getting regular exercise can also help manage disease.

Choosing right therapy for diabetes depends on kind of diabetes, and With their 2018 proposal, American Diabetes Association established following categorization[5]:

- Type 1 diabetes mellitus : cause complete insulin insufficiency, often brought on by autoimmune-cell destruction;
- Type 2 diabetes mellitus : in response to insulin resistance, which is often accompanied by a gradual decline in -cell insulin secretion;
- Gestational diabetes mellitus: gestational diabetes mellitus, first detected in the second or third trimester of pregnancy but not evident at start of the pregnancy;
- Distinct forms of diabetes caused by other factors, for instance, monogenic diabetes syndromes, drug-or chemical-induced diabetes (like after using glucocorticoids, or receiving an organ transplant, treating HIV/AIDS,) and exocrine pancreas diseases (like pancreatitis and cystic fibrosis)

2. EPIDEMIOLOGY

Forecasts indicate that 366 million people would have diabetes in 2011, with that figure rising to 552 million by 2030. Despite a global uptick, 80% of world's people living with type 2 diabetes live in countries with low or medium incomes. In 2011, diabetes had a fatal impact on 4.6 million people.[6] Millions of individuals will get type 2 diabetes by 2030, according to estimations. Geographical variations in prevalence of type 2 diabetes mellitus are mostly attributable to differences in environmental and lifestyle risk factors.[7] In the next 20 years, there is expected to be a significant increase in the incidence of diabetes in adults, with type 2

DM becoming more common. Patients in developing countries, where the average age is 45–64, are likely to account for the bulk of this expansion[8] explained in Fig.1.

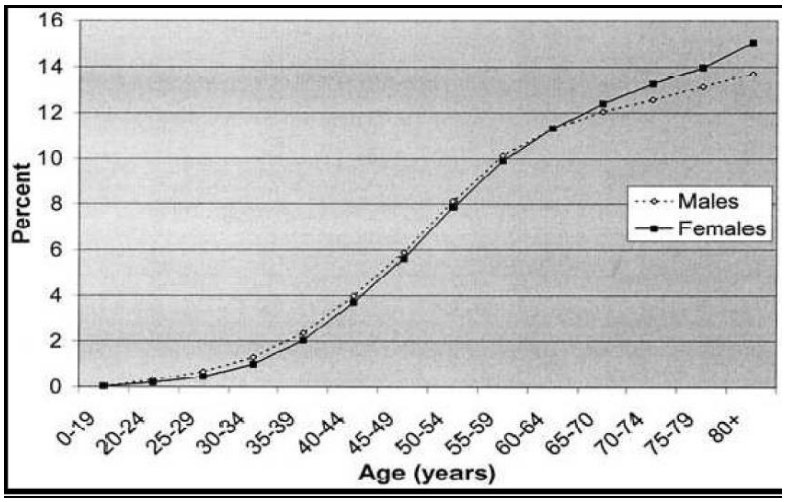

Fig. 1: A global view: Epidemiology of diabetes.

3. Pathophysiology and definition of diabetes in general

Diabetes has a complicated pathophysiology and definition, and in recent years, hormonal discoveries have added to the complexity of the disease. Generally speaking, diabetes may be divided into the subsequent groups.[9,10]:

A combination of insulin resistance and a slow loss of insulin secretion leads to T2D, On the other hand, is characterized by insulin shortage, which develops when beta cells die off. This spectrum encompasses a variety of: Gestational diabetes mellitus (pregnant women with non-overt diabetes who had their diagnosis made in second or third trimester) and specific types of diabetes due to other causes, e.g. pancreatic exocrine disease (conditions like cystic fibrosis), monogenic diabetes syndromes (such as diabetes mellitus type 1 in infants and young adults) and diabetes caused by drugs or chemicals (for example, after an organ donation or during HIV/AIDS therapy).[9,10]

Type 1 diabetes is an autoimmune disease that lasts for a long time, disease that arises from the gradual death of insulin-producing pancreatic β-cells by T-cells. Other than the process of declining β-cell mass causes the β-cells to gradually lose their sensitivity to glucose, which in turn leads to low insulin levels and hyperglycemia.[9,11,12] T1DM typically manifests in youth, with the most common years being 10–14.[13] Environmental factors and triggers, along with a genetic risk that predisposes the patient, interact intricately in development of T1D.[14]

Genetics primarily have a role in development of β-cell auto-immunity, particularly in those who possess one or both of the haplotypes associated with the presentation of the human leukocyte antigen class 2. Research on first-degree relatives has shown that type 1 diabetes may be predicted by presence of two or more autoantibodies that target β-cells. Antibody detection age and antibody quantity determine illness progression; its accuracy and antibody concentration.[9,10,11] Infections, changes in food, psychological and social stress, and changes in makeup of the gut microbiome are all environmental variables that might set off auto-immunity.[15]

Secondary bile acids, which interact through farnesoid receptor X, or FXR, become signaling molecules after they are recycled back into the bloodstream, participate in control of glucose homeostasis.[15] An insulin-deficiency metabolic disorder that develops over time as a result of both tissue insulin resistance and insufficient compensatory mechanisms, Type 2 Diabetes accounts for over 90% of all diabetes cases. Unsustainable blood glucose levels have the potential to cause diabetic issues down the road.[16] Overconsumption of sugar and lipids in diet may eventually lead to β-cell inflammation and stress, which in turn causes malfunction and further stage atrophy. At time of diagnosis, β-cell loss is seen in up to 50% of cases. Insulin resistance lowers blood sugar in the body's outer tissues such as absorption in liver, muscle, and adipose tissue and increases glucose synthesis in liver.[17] Insulin resistance is worse in obese individuals with hypertrophic adipose tissue via secreting more pro-inflammatory cytokines and free fatty acids. A persistent mild inflammatory state is a key component in pathogenesis of type 2 diabetes[16] explained in Fig.1.

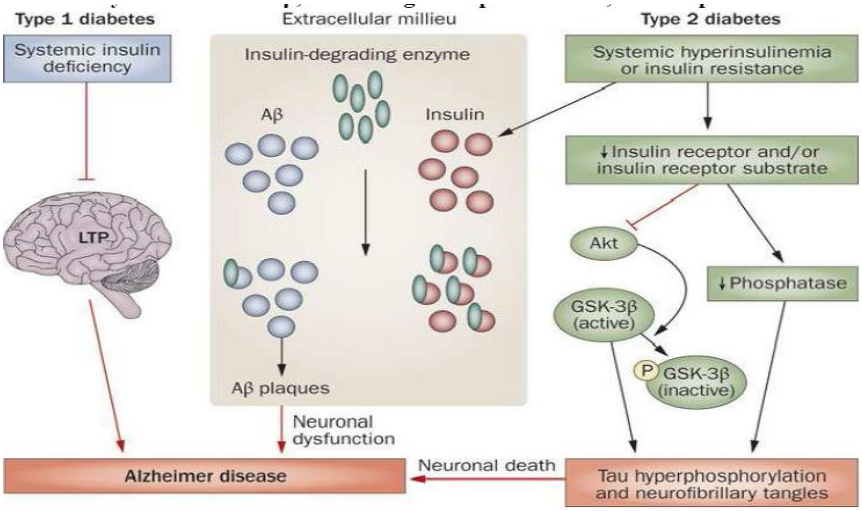

Fig. 1: Pathophysiology of Type I and Type II diabetes.β- Amyloid, LTP- long term potentiation, P- Phosphate, GSK-3β-glycogen synthase kinase 3β.

4. The consequences of diabetic mellitus

Diabetes has a substantial correlation with ischemic heart disease and other macrovascular problems. Illness, peripheral vascular disease, cerebrovascular disease, and microvascular consequences, such as neuropathy, nephropathy, and retinal degeneration. About one-third to half of diabetic patients experience organ and tissue damage as a result.[18] Multi-organ dysfunction is caused by anatomical, structural, and functional abnormalities in the blood vessels that are linked to diabetes.[19] Target glycated haemoglobin (A1C) selection has to be customized according to the patient's functional status and comorbidities. Patients with long-standing type 2 diabetes who are at high risk for cardiovascular disease (CVD) may be better off with a target A1C of 7.0 to 7.9% rather than less than 6.0%, according to Action to Control Cardiovascular Risk in Diabetes study.[20] Research indicates that among patients with newly diagnosed type 2 diabetes, there is a sustained decrease in the risk of myocardial infarction and other diabetes-related complications, mortality, as well as total mortality following an intense control (A1C 7%).[21,22] Patients with type 2 diabetes have a decreased risk of microvascular problems when their glycaemic management is improved.[23,20,24-27] As the condition worsens, tissue or vascular damage develops, which can result in serious diabetes consequences such ulceration, neuropathy, retinopathy, and nephropathy. Patients with type 1 diabetes for an extended period of time are vulnerable to macrovascular disease (coronary disorders of the heart, arteries, and peripheral vessels). Large artery atherosclerosis, which is frequently linked to obesity, hypertension, and hyperlipidemia, is a substantial determinant of type 2 diabetes. Chronic kidney disease and cardiovascular comorbidities account for majority of type 2 diabetes deaths.[28]

5. Diagnosis

American Diabetes Association (ADA) states that fasting blood sugar level has to be utilized in regular diabetes screening; however, glucose tolerance, random blood sugar, and postprandial blood sugar should also be considered. Tests are also utilized to determine blood sugar levels. One or more of the following criteria must be met in order to diagnose diabetes:

- Polyurea, polydipsia, inexplicable weight loss, and other diabetes symptoms, in addition reaching a plasma glucose level of 11.1 mmol/L (200 mg/dL) on an as-needed basis.
- After 8 hours of fasting, a normal range for fasting plasma glucose is 70-110 mg/dl.

Similar to ADA, the World Health Organization classifies diabetes mellitus based on its etiological kinds as well as its clinical phases, which include impaired glucose

tolerance/impaired fasting glucose, diabetes, and normoglycemia. However, the WHO group also contains the classification that was previously known as

Fasting glucose levels of 7.0 mmol/L (126 mg/dL) and/or 2.-hour glucose levels of 7.8 mmol/L (140 mg/dL) following a 75-g OGTT 4 are indicative of gestational impaired glucose tolerance (GIGT) and GDM.[28]

6. TREATMENT

6.1 lifestyle adjustments and risk factor management

Everyone agrees that leading a healthy lifestyle is essential for managing diabetes, including preventing type 2 diabetes.[29] Taking up constructive self-care techniques, activity, a nutrient-rich diet, and blood glucose monitoring are essential for the advancement of the disease.[30] The three primary modifiable risk factors for diabetes that fall under the category of healthy living are diet, alcohol consumption, and smoking. Each of these is covered in turn.

1) Smoking

Numerous conditions, including cardiovascular disease, have been linked to smoking as a risk factor. In spite of the substantial amount of literature, the precise mechanism because the pathophysiological relationship that exists between diabetes, smoking, and glucose homeostasis is still unclear.[31,32] Research indicates that smoking worsens the prevalent diseases linked to diabetes and raises the risk of diabetes and death.[33,34] Microvascular problems include retinopathy, neuropathy, and nephropathy are impacted by smoking. Research indicates that smoking can raise the likelihood of Neuropathy is more common among smokers who have type 1 or type 2 diabetes, according to a meta-analysis of 19 observational studies. There was a documented occurrence and progression of neuropathy, especially in individuals with type 1 diabetes.[32]

2) Alcohol

A comprehensive evaluation of 13 research found that alcohol (ethanol) is a risk factor for hypoglycemia in people with type 1 diabetes. demonstrated that drinking alcohol should only be done in conjunction with food consumption.[35] Studies on type 2 diabetes indicate using alcohol in moderation may provide certain health benefits, such as a reduced risk of cardiovascular disease and mortality[36], together with the prevalence of diabetes in several investigations; yet, favorable health habits may be severely affected by heavy and/or

excessive alcohol use. Drinking alcohol, in any quantity, may impair adherence to prescribed nutrition, medicine, exercise, and glucose self-monitoring plans.[30] Or Heavy drinkers are more likely to develop diabetes; other factors that influence results include the kind of alcohol consumed, gender, and body mass index.[37]

3) DIET

Understanding diabetes has traditionally revolved around diet, with early reports linking the disease's symptoms to the consumption of sugary foods. and carbohydrates.[38] Reducing the risk of diabetes and cardiovascular disease (CVD) by encouraging a balanced diet is the aim of diet in diabetes (type 1 and type 2). The American Diabetes Association (ADA) suggests a diet to reach and maintain blood glucose levels in a normal range while avoiding or reducing the pace of diabetic complications; cholesterol and lipoprotein profile that minimizes the risk of vascular disease; controlled blood pressure.[39]

6.2 Pharmaceuticals, gastric bypass, and metabolic surgery

Medication is typically the second line of treatment if lifestyle changes are not producing adequate results, in particular sulfonylureas and metformin (for type 2 diabetes). Insulin replacement therapy is the recommended course of treatment for type 1 diabetes.[11,10] Given the evolving field of pharmacology and the growing comprehension of mechanism for diabetic remission Globally, diabetes is becoming more common, with type 2 diabetes accounting for majority of occurrences. Patients undergoing surgery who are both overweight and have type 2 diabetes are more likely to get therapy for both conditions because of the established link between the two. Obesity and other metabolic disorders are linked to type 2 diabetes (T2DM), which increases morbidity, mortality, and cost burden. Based on weight loss and comorbidity resolution, Bariatric surgery (BS) has been shown to be the most effective therapy for obesity in randomized controlled trials (RCTs).More recently, surgery has been shown to be more effective than the best medical therapy alone in reducing hyperglycemia.[40,41]

The mechanisms appear to involve improvements regarding insulin production, insulin responsiveness, and incretin profiles in addition to the amount of weight reduction alone. When compared to persons with higher BMIs, MS provides comparable benefits to those with a BMI between 30 and 35 kg/m2. The effects of nonhormonal and gut hormones variables on glucose metabolism and weight reduction are now better understood. The STAMPEDE (Surgical Treatment and Medications Potentially Eradicate Diabetes

Efficiently) trial's five-year follow-up study was one of first to offer level I data regarding effectiveness of BS in T2DM control and remission.[41]

The goal of insulin therapy should be to emulate nature, which has remarkable efficacy in preventing hypoglycemia in between meals and controlling postprandial hyperglycemia.[42] Insulin injection sites can be intramuscular or intravenous, and both are crucial for the optimal and safe functioning of the drug path. There are various forms of insulin available, including human, cow, and hog insulin.

There are drawbacks and dangers to insulin therapy. When an incorrect amount of insulin is taken when meals and insulin injections are not timed correctly, Weight gain and hypoglycemia are the most notable adverse effects.[43,44]

6.3 Herbal treatment of diabetes

Numerous herbal treatments for diabetes and its consequences have been proposed. The primary components of these mixtures are medicinal herbs. Table 1 provides a list of medicinal plants with antidiabetic and related therapeutic effects.[45]

Table 1: Indian medicinal herbs that have antidiabetic and other useful effects.

Plant Name	Antidiabetic and other beneficial effects in traditional medicine	Ayurvedic/common name/herbal formulation	References
Annona squamosa	Hypoglycemic and antihyperglycemic activities of ethanolic leaf-extract, Increased plasma insulin level	Sugar apple	[46-48]
Artemisia pallens	Hypoglycemic, increases peripheral glucose utilization or inhibits glucose reabsorption	Davana	[49]
Areca catechu	Hypoglycemic	Supari	[50]
Beta vulgaris	Increases glucose tolerance in OGTT	Chukkander	[51]
Hibiscus rosa-Sinesis	Initiates insulin release from pancreatic beta cells	Gudhal or Jasson	[52]

Table 2: Formulated Herbal Drugs with antidiabetic properties.

Drug	Ingredients	Company
Diabecon	*Gymnema sylvestre, Pterocarpus marsupium, Glycyrrhiza glabra, Casearia esculenta, Syzygium cumini, Asparagus racemosus, Boerhavia diffusa, Sphaeranthus indicus, Tinospora cordifolia, Swertia chirata, Tribulus terrestris, Phyllanthus amarus, Gmelina arborea, Gossypium herbaceum, Berberis aristata, Aloe vera,* Triphala, *Commiphora wightii*, shilajeet, *Momordica charantia, Piper nigrum, Ocimum sanctum, Abutilon indicum, Curcuma longa, Rumex maritimus*	Himalaya
Bitter gourd Powder	Garry and Sun natural Remedies	Garry and Sun natural Remedies
Gurmar powder	Gurmar (*Gymnema sylvestre*)	Garry and Sun natural Remedies
Dia-care	Sanjeevan Mool; Himej, Jambu beej, Kadu, Namejav, Neem chal.	Admark Herbals Limited
Epinsulin	Swastik Formulations	Swastik Formulations

7. INSULIN-RESISTANT DIABETES MELTUS DRUG TARGETS

Most current treatment approaches predate either a thorough understanding of disease pathophysiology or identification of specific biological targets. Many molecular therapeutic targets involving different metabolic processes have been identified in the recent few years. Based on their expected contributions to changing one or more critical components of etiology of diabetes and metabolic syndrome, these include: 1) reducing glucose overproduction by the liver; 2) focusing on beta cells; 3) emphasising routes involved in insulin signaling; and 4) with an emphasis on lipid metabolism.

1) lessening the liver's overproduction of glucose

The liver is crucial in controlling the synthesis or breakdown of glycogen to control endogenous glucose production through the processes of gluconeogenesis and glycogenolysis. Higher hepatic glucose synthesis rates are primarily accountable for the overt

hyperglycemia's development. Glucagon induces the glycogenolytic and gluconeogenesis pathways, which leads to hyperglycemia.[53,54] Small-molecule antagonists may be developed to target its receptor, a seven-transmembrane-domain Gprotein receptor.[55]

2) Treating beta cells

Human insulin secretion can be enhanced by the administration of any one of these two hormones. Dipeptidylpeptidase-IV (DP-IV) can rapidly degrade both hormones' amino terminals, hence it has been suggested to use enzyme-resistant GLP-1 peptide agonists that have undergone modification. It has been noted that DP-IV deficient mice have improved insulin production, elevated levels of circulating active GLP-1, and an otherwise normal phenotype.[56] Thus, novel treatment options that circumvent sulphonylurea side effects including hypoglycemia, weight gain, and subsequent failures are likely to emerge from the development of GLP-1 analogues and DP-IV inhibitors.

3) Targeting the insulin signaling pathways

Insulin receptor-tyrosine kinase and insulin-stimulated phosphatidylinositol-3-OH kinase activation are two examples of the several signal transduction errors that can lead to insulin resistance. Many molecular targets are now being researched as potential means of improving the signal transduction mediated by insulin. Patients that are insulin resistant have been found to have elevated expression of PTP 1B.[57] The activation of insulin receptor kinase is inhibited by this enzyme's overexpression. Compared to its littermates, a PTP 1B knockout mouse showed greater insulin sensitivity. Therefore, PTP 1B inhibition is a promising target for therapeutic development.[58]

4) Targeting lipid metabolism

In order to cure type 2 diabetes, it will be very beneficial to reduce appetite and/or increase energy expenditure because obesity is a major factor in the development of insulin resistance. MCR-4, or the melanocortin-4 receptor, provides the likelihood of reducing type 2 diabetes and obesity. Therefore, a robust phenotype exhibiting several metabolic syndrome features is caused by either a rise in expression of a natural MCR4 antagonist or an absence of receptor itself.[59,60] mentioned in Table.3.

Table 3: Current treatment drugs and their molecular target for type-2 diabetes.

Drug class	Sites of action	Adverse events	Molecular target
Insulin	Liver, muscle, fat	Hypoglycemia, weight gain	Insulin receptor
Sulphonylureas (e.g. glibenclamide) plus nateglimide and repaglimide	Pancreatic β cell	Hypoglycemia, weight gain	SU receptor/K+ ATP channel
Metformin (biguanides)	Liver (muscle)	Gastrointestinal disturbance lactic acidosis	Unknown
Acarbose	Intestine	Gastrointestinal disturbances	α-Glucosidase

8. CONCLUSION

When untreated, all of the metabolic conditions together referred to as diabetes mellitus cause an abnormally high blood glucose content. Type 1 diabetes occurs when the pancreas ceases to generate appreciable levels of the hormone insulin, typically as a result of the autoimmune destruction of the pancreatic beta cells that produce insulin. Contrarily, diabetes mellitus type 2 is currently believed to be caused by insulin resistance or autoimmune attacks on the pancreas. A person with type 2 diabetes may have normal, or even unusually high, insulin production from their pancreas. Restoring normal glucose metabolism is the major objective of managing diabetes, to the extent feasible. Individuals with a complete insulin shortage need insulin replacement therapy, which comes in the form of injections or pills, in order to accomplish this goal. However, if you want to overcome insulin resistance, you should start by changing your diet and exercising more. Additional goals of diabetes management include reducing or controlling the many adverse consequences of both the disease and its treatment. Diabetes can be a patient's friend and source of delight if the blood sugar level is kept under control. Diabetes mellitus has a significant morbidity and mortality rate due to its complex multifactorial nature. With the introduction of more advanced medications and surgical alternatives, The physiology of diabetes and our understanding of it have gradually expanded. Nevertheless, despite our growing understanding, we are still unable to fully comprehend its pathophysiology, making it challenging to make a new classification based on the available research. Hopefully, future studies will direct medical professionals toward the best surgical and/or medical treatments for diabetes and offer more framework for a possible reclassification of the condition. Because of their anti-diabetic properties, which include flavonoids, tannins, phenolic acid, and alkaloids that enhance pancreatic tissue function by either secreting more insulin or reducing intestinal glucose absorption, ants are natural

antioxidants and potent herbal remedies. To analyze the medicinal qualities of plants, more research is required to isolate the active ingredients and understand the molecular interactions of their molecules.

9. Future prospect

Overall, while diabetes presents significant challenges, ongoing research and innovation offer hope for improving outcomes and quality of life for individuals living with the disease. However, realizing these future prospects will require collaborative efforts from healthcare providers, researchers, policymakers, industry stakeholders, and the broader community. Research in diabetes management is ongoing, with a focus on developing more effective medications, such as better insulin formulations, incretin-based therapies, and novel classes of drugs that target different aspects of glucose metabolism. Additionally, advancements in gene therapy and stem cell research hold promise for potential cures or long-term treatments.

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