Journal of Biosciences and Medicines, 2025, 13(7), 121-130
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Review on the Treatment Progress of Type 2 Diabetes Mellitus

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How to cite this paper: Liu, M.X., Zhou, H.D., Huang, S., Zhang, W.Z., Xu, J.H., Xin, X.D. and Yu, D.B. (2025) Review on the Treatment Progress of Type 2 Diabetes Mellitus. *Journal of Biosciences and Medicines*, **13**, 121-130.
https://doi.org/10.4236/jbm.2025.137009

Received: May 30, 2025
Accepted: July 11, 2025
Published: July 14, 2025

Abstract

Type 2 diabetes mellitus (T2DM) is a common chronic metabolic disease, and its incidence is on the rise globally. This article comprehensively reviews the treatment progress of T2DM, covering multiple aspects such as lifestyle interventions, drug therapy, surgical treatment, cell therapy and gene therapy, as well as other emerging treatment methods. It elaborates in detail on the action mechanisms, clinical application effects, advantages, and limitations of various treatment approaches, aiming to provide comprehensive treatment references for clinicians and promote the improvement of the treatment level of T2DM.

Keywords

Lifestyle Intervention, Pharmacotherapy, Surgical Treatment, Molecular Therapy

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic hyperglycemia syndrome caused by both insulin resistance and insufficient insulin secretion. Its onset is closely related to multiple factors such as genetics, environment, and lifestyle [1] [2]. In recent years, with the increase in the global obesity rate and the acceleration of the aging process, the incidence of T2DM has been continuously rising, and it has become a public health problem that seriously threatens human health. T2DM not only causes abnormal blood sugar but is often accompanied by various complications,

such as cardiovascular diseases, kidney diseases, neuropathies, retinopathies, etc., which seriously affect the quality of life and lifespan of patients. Therefore, continuously exploring and optimizing the treatment methods for T2DM has important clinical significance and social value.

2. Lifestyle Interventions

2.1. Diet Management

2.1.1. Traditional Diet Principles

For a long time, controlling total energy intake and ensuring a balanced diet have been the basis of dietary treatment for T2DM. Patients are advised to reduce the intake of refined carbohydrates (such as white bread and white rice) and increase the intake of dietary fiber (such as whole grains, vegetables, and fruits). Dietary fiber can delay the absorption of carbohydrates, reduce postprandial blood sugar peaks, and at the same time improve the intestinal flora and promote intestinal health. In addition, a low-fat and low-salt diet helps to control weight and blood pressure and reduce the risk of cardiovascular diseases.

2.1.2. Emerging Diet Patterns

Low-Carbohydrate Diet: In recent years, the low-carbohydrate diet has received attention in the treatment of T2DM. This diet pattern makes the body rely more on fat for energy by restricting carbohydrate intake. Studies have shown that a low-carbohydrate diet can significantly reduce blood sugar levels, reduce the dosage of hypoglycemic drugs, and at the same time help with weight loss. However, long-term adoption of a low-carbohydrate diet may lead to nutritional imbalance and an increased risk of cardiovascular diseases. Therefore, it needs to be used rationally under the guidance of a doctor.

Intermittent Fasting: Intermittent fasting is a time-restricted eating pattern, including the 16:8 fasting method (fasting for 16 hours and eating for 8 hours per day) and the 5:2 fasting method (eating normally for 5 days and restricting food intake for 2 days per week). Research has found that intermittent fasting can improve insulin sensitivity, regulate metabolic rhythms, and reduce blood sugar and weight. In addition, intermittent fasting can also reduce oxidative stress and inflammatory responses, which is beneficial to cardiovascular health. However, the elderly, pregnant women, lactating women, and patients at risk of hypoglycemia should use intermittent fasting with caution.

2.2. Exercise Therapy

2.2.1. Regular Exercise

Regular physical exercise is an important part of the comprehensive treatment of T2DM [3]. Exercise can increase the uptake and utilization of glucose by muscles, improve insulin sensitivity, and reduce blood sugar levels. At the same time, exercise can also help with weight loss, improve cardiovascular function, lower blood pressure and blood lipids, and reduce the risk of cardiovascular diseases. It is recommended that T2DM patients engage in at least 150 minutes of moderate-

intensity aerobic exercise per week, such as brisk walking, jogging, swimming, and cycling. They can also appropriately perform strength training, such as weightlifting and push-ups.

2.2.2. Micro-Exercise

In addition to traditional exercise methods, the concept of micro-exercise has gradually emerged. Micro-exercise refers to adding some short-term and mild physical activities in daily life, such as walking up and down stairs, standing while working, and getting up and moving regularly. These seemingly insignificant activities can accumulate to increase energy consumption and promote glucose metabolism. Studies have shown that micro-exercise can improve blood sugar control in T2DM patients and improve their quality of life.

3. Drug Therapy

3.1. New Applications and Improvements of Traditional Drugs

Metformin: Metformin is a first-line drug for the treatment of T2DM and has multiple action mechanisms [4]. In addition to reducing blood sugar by inhibiting hepatic glucose output and increasing the uptake and utilization of glucose in peripheral tissues, recent studies have found that metformin can improve the intestinal flora, increase the number of beneficial bacteria, and reduce the growth of harmful bacteria, thereby regulating the intestinal endocrine function, reducing the inflammatory response, and having a positive impact on the treatment of T2DM. In addition, metformin also has a cardiovascular protective effect and can reduce the risk of cardiovascular diseases.

Sulfonylureas: Sulfonylureas lower blood sugar by stimulating insulin secretion from pancreatic β-cells. With the in-depth research, new sulfonylureas have been continuously developed. While maintaining hypoglycemic effects, their risk of hypoglycemia has decreased [5]. For example, compared with traditional sulfonylureas, glimepiride has advantages such as a long-acting effect and a low incidence of hypoglycemia. In addition, some sulfonylureas can also improve insulin resistance, helping to enhance the treatment effect.

3.2. New Hypoglycemic Drugs

Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors: SGLT2 inhibitors lower blood sugar levels by inhibiting the reabsorption of glucose in the proximal convoluted tubules of the kidneys and promoting urinary glucose excretion. This class of drugs not only has significant hypoglycemic effects but also has additional benefits such as weight loss, blood pressure reduction, blood uric acid reduction, and cardiovascular and renal protection [6]. A large number of clinical studies have confirmed that SGLT2 inhibitors can reduce the risk of cardiovascular diseases and the hospitalization rate for heart failure in T2DM patients and also have a protective effect on the kidneys, which can delay the progression of diabetic nephropathy. Common SGLT2 inhibitors include dapagliflozin, empagliflozin,

canagliflozin, etc. [6] [19] [20].

Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists: GLP-1 is a peptide hormone secreted by intestinal L cells and has multiple physiological functions. GLP-1 receptor agonists act by binding to GLP-1 receptors, including the following effects: promoting insulin secretion, and this insulin-promoting effect is glucose-concentration-dependent, that is, the effect is enhanced when blood sugar is high and weakened when blood sugar is low, thus reducing the risk of hypoglycemia [7]; inhibiting glucagon secretion and reducing hepatic glucose output; delaying gastric emptying, increasing satiety, and reducing food intake, which helps with weight loss; and also having effects such as protecting the cardiovascular system, improving endothelial function, and reducing the inflammatory response. GLP-1 receptor agonists are divided into short-acting and long-acting preparations. Short-acting preparations such as exenatide need to be injected twice a day, while long-acting preparations such as liraglutide and semaglutide only need to be injected once a week, and patients have better compliance.

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors: DPP-4 inhibitors exert hypoglycemic effects by inhibiting the activity of DPP-4 enzyme, reducing the degradation of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), and thus increasing the levels of endogenous GLP-1 and GIP [8]. DPP-4 inhibitors have good hypoglycemic effects, a low risk of hypoglycemia, do not cause weight gain, and may also have a certain protective effect on the cardiovascular system [8]. Common DPP-4 inhibitors include sitagliptin, saxagliptin, vildagliptin, etc.

4. Surgical Treatment

4.1. Gastrointestinal Metabolic Surgery

4.1.1. Surgical Methods and Principles

Gastrointestinal metabolic surgeries mainly include Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion with duodenal switch (BPD-DS), sleeve gastrectomy (SG), and other surgical procedures. These surgeries all aim to change the anatomical structure of the gastrointestinal tract, deeply affect the digestion and absorption process of food, and thus achieve the dual goals of reducing blood sugar and losing weight [9].

Taking the Roux-en-Y gastric bypass (RYGB) as an example, this surgery precisely divides the stomach into a proximal small gastric pouch and a distal large gastric pouch, and then anastomoses the small intestine with the proximal small gastric pouch. In this way, food can bypass most of the stomach and the duodenum, greatly reducing the amount of nutrient absorption. At the same time, the surgery also causes significant changes in the secretion of intestinal hormones. Notably, the secretion of glucagon-like peptide-1 (GLP-1) increases significantly [10], which plays a crucial role in improving insulin sensitivity and has a positive impact on the metabolic status of T2DM patients from multiple aspects [10].

4.1.2. Clinical Application Effects

Numerous clinical research data have clearly shown that gastrointestinal meta-

bolic surgery has remarkable effects in the treatment of obese T2DM patients [11] [12]. After surgery, patients' blood sugar levels can often drop rapidly, and some patients can even achieve complete remission of diabetes, which means that they no longer need hypoglycemic drugs, and their blood sugar can still be stably maintained within the normal range.

In addition to the significant blood sugar control effect, the surgery can also play a key role in weight loss in patients. At the same time, it can effectively improve a series of metabolic disorders closely related to obesity, such as hypertension and hyperlipidemia, which will be alleviated to varying degrees, thus greatly reducing the risk of cardiovascular diseases and comprehensively improving the health level and quality of life of patients.

However, we must be clearly aware that gastrointestinal metabolic surgery is not without risks. Surgical complications such as bleeding, infection, and anastomotic leakage may occur [13] during the operation [13]. After the operation, patients may also face health risks such as malnutrition and deficiencies of vitamins and trace elements. Therefore, in clinical practice, it is necessary to strictly control the surgical indications, conduct comprehensive and detailed preoperative evaluations of patients, and provide scientific and standardized postoperative management to ensure the safety and effectiveness of surgical treatment and enable patients to benefit maximally from the surgery.

4.2. Pancreatic and Islet Transplantation

Islet Transplantation: Islet transplantation involves transplanting healthy islet cells into patients to restore islet function, enabling patients to no longer rely on insulin injections. Islet transplantation is mainly applicable to patients with type 1 diabetes mellitus and some carefully selected T2DM patients, especially those with extremely poor blood sugar control and severe complications. With the continuous improvement of transplantation techniques and immunosuppressive drugs, the success rate and safety of islet transplantation have increased [14]. However, islet transplantation also faces some problems, such as donor shortages, immune rejection reactions, and side effects caused by long-term use of immunosuppressive drugs.

Pancreas Transplantation: Pancreas transplantation involves transplanting the entire pancreas into patients and is applicable to patients with type 1 diabetes mellitus complicated by renal failure or other severe complications. Pancreas transplantation can simultaneously restore insulin secretion and blood sugar regulation functions and improve the quality of life of patients. However, pancreas transplantation has a large surgical trauma, many postoperative complications, and severe immune rejection reactions. It requires long-term use of immunosuppressive drugs, so its clinical application is limited to a certain extent.

5. Cell Therapy and Gene Therapy

5.1. Stem Cell Therapy

Mesenchymal Stem Cell Therapy: Mesenchymal stem cells (MSCs) are adult stem

cells with multi-directional differentiation potential and immunomodulatory functions. In recent years, research on the treatment of T2DM with MSCs has made certain progress [15]. MSCs can differentiate into islet-like cells to replace damaged pancreatic β-cells and secrete insulin. They can also secrete a variety of cytokines and growth factors through paracrine effects, improve the islet microenvironment, promote the proliferation and survival of pancreatic β-cells, and improve insulin sensitivity. A number of clinical studies have confirmed the safety and effectiveness of MSC treatment for T2DM [15]. For example, a clinical study conducted by the team of Chinese People's Liberation Army General Hospital showed that umbilical cord mesenchymal stem cell transplantation can significantly reduce the demand for exogenous insulin in T2DM patients, improve blood sugar control, and relieve insulin resistance.

Other Stem Cell Therapies: In addition to MSCs, other types of stem cells, such as embryonic stem cells and induced pluripotent stem cells, have also received attention in the research on the treatment of T2DM. Embryonic stem cells have totipotency and can differentiate into various cell types. However, due to ethical controversies and immune rejection issues, their clinical application is limited. Induced pluripotent stem cells are pluripotent stem cells reprogrammed from somatic cells to have the characteristics of embryonic stem cells. Theoretically, they can be used for the treatment of T2DM, but they are still in the research stage and face technical challenges and safety risks.

5.2. Gene Therapy

Gene Editing Technology: Gene editing technologies such as the CRISPR/Cas9 system bring new hope for the treatment of T2DM. By editing genes related to T2DM, such as genes related to the insulin signaling pathway, the development and function of pancreatic β-cells, etc., it is expected to improve the function of pancreatic β-cells and insulin sensitivity, thereby achieving the goal of treating T2DM [16]. However, the application of gene editing technology in the treatment of T2DM still faces many challenges, such as the accuracy and safety of gene editing, off-target effects, and ethical issues, and requires further in-depth research.

Gene Delivery Therapy: Gene delivery therapy involves introducing beneficial genes into patients to correct or compensate for gene defects. For example, insulin genes or genes that regulate insulin secretion are introduced into tissues such as the liver and muscles through vectors such as adeno-associated viruses (AAVs), enabling them to express insulin or related regulatory factors, thereby reducing blood sugar. Currently, gene delivery therapy for T2DM is still in the early stages of animal experiments and clinical trials. It is necessary to further optimize gene vectors and treatment plans to improve treatment efficacy and safety.

6. Other Treatment Aspects

6.1. Immunotherapy

6.1.1. Pathogenesis and Immune Abnormalities

More and more studies have shown that the onset of T2DM is closely related to

immune system abnormalities [17]. In T2DM patients, there is a chronic low-grade inflammatory response. Immune cells such as macrophages and T lymphocytes are activated and release a variety of inflammatory factors, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). These inflammatory factors can lead to insulin resistance and impaired pancreatic β-cell function. In addition, autoimmune reactions may also be involved in the pathogenesis of T2DM. Islet autoantibodies can be detected in some T2DM patients, suggesting that autoimmune reactions may lead to the destruction of islet cells.

6.1.2. Immunotherapy Strategies

Based on the immune pathogenesis of T2DM, immunotherapy has become a research hotspot. Immunotherapy mainly includes the use of antibodies, cell therapy, vaccines, and other methods to intervene in the patient's immune system, reduce inflammatory reactions and autoimmune damage, and protect pancreatic β-cell function. For example, the use of TNF-α antagonists can reduce the level of inflammatory factors and improve insulin resistance; regulatory T-cell therapy can protect pancreatic β-cells by inhibiting the immune response; and the development of vaccines against islet autoantigens is expected to induce immune tolerance and prevent the destruction of islet cells by autoimmune reactions. However, currently, the application of immunotherapy in the treatment of T2DM is still in the early stage, and further in-depth research is needed on its safety and effectiveness.

6.2. Closed-Loop Insulin Infusion System

6.2.1. System Composition and Working Principle

The closed-loop insulin infusion system, also known as the "artificial pancreas," is a new type of insulin treatment device. It mainly consists of a continuous glucose monitoring system (CGM), an insulin pump, and a control algorithm [18]. The CGM monitors the patient's blood sugar level in real-time and transmits the data to the control algorithm. The control algorithm automatically adjusts the insulin infusion volume of the insulin pump according to the preset blood sugar target value and the patient's blood sugar changes, achieving automatic blood sugar regulation.

6.2.2. Clinical Application Effects

Clinical studies have shown that the closed-loop insulin infusion system [18] can make the blood sugar control of T2DM patients more precise and stable, reducing the risk of blood sugar fluctuations and hypoglycemia. At the same time, the system can also improve the quality of life of patients, reducing their psychological burden and self-management pressure. However, the closed-loop insulin infusion system [18] still has some limitations, such as high equipment costs, the need for regular calibration and maintenance, and the possibility of malfunctions, which limit its wide application.

7. Conclusion

In conclusion, significant progress has been made in the treatment of T2DM.

From traditional lifestyle interventions and drug therapies to emerging surgical treatments, cell therapies, gene therapies, and immunotherapies, more treatment options are available for T2DM patients. Lifestyle interventions, as the basic treatment measures, should be used throughout the treatment of T2DM. The continuous innovation of drug therapies has led to the emergence of new hypoglycemic drugs such as SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors, which not only have good hypoglycemic effects but also have additional benefits such as cardiovascular and renal protection. Surgical treatment has a significant therapeutic effect on obese T2DM patients, but it is necessary to strictly master the surgical indications and do a good job in perioperative management. Cell therapy and gene therapy bring new hope for the treatment of T2DM, but they still face many technical challenges and safety issues and require further in-depth research. Emerging treatment methods such as immunotherapy and closed-loop insulin infusion systems [18] are also constantly being explored and developed. In the future, the treatment of T2DM will develop towards the direction of personalization, precision, and comprehensiveness. Clinicians should formulate reasonable treatment plans according to the specific conditions of patients to improve the treatment effect [6] [19] [20].

Funding

This paper is supported by Innovation Project of Guangxi Graduate Education (YCSW2024524 and YCSW2024537).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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