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Comprehensive Management of Type 2 Diabetes Mellitus: From Basic Research to Clinical Application

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Abstract. Type 2 diabetes mellitus (T2DM) is a global metabolic disease with complex pathophysiological mechanisms, characterized mainly by insulin resistance and pancreatic β-cell dysfunction. Recent studies have focused on revealing the role of insulin signaling, lipid metabolism, and inflammatory responses in the pathogenesis of T2DM. Despite the large number of studies, the comprehensive management of T2DM remains challenging, especially in terms of individualized treatment and prevention of complications. This article provides a comprehensive analysis of the pathophysiological mechanisms of T2DM and their application in clinical management, analyzing them from epidemiological and pathophysiological perspectives, exploring the molecular and genetic mechanisms of their operation, and evaluating the effectiveness of current therapeutic approaches. It was found that improving insulin sensitivity and regulating lipid metabolism are key strategies for the management of T2DM.The comprehensive management of Type 2 diabetes (T2D) can be based on the important theoretical basis provided by this study, pointing out the limitations of current treatments, and future research should focus on the development of novel drugs and the integrated application of lifestyle interventions to better control disease progression and reduce complications.

Keywords: Type 2 diabetes mellitus, Insulin resistance, Pathophysiology

1. Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease marked by elevated blood glucose, the cause of which has not yet been fully clarified. Insulin resistance (IR) and pancreatic β-cell dysfunction are the features of this disease. It is frequently the primary manifestation of metabolic dysfunction syndrome (MDS), along with various metabolic disorders like hyperglycemia, dyslipidemia, obesity, and nonalcoholic fatty liver disease (MASLD), etc [1]. T2DM may also be accompanied by cardiovascular disease (CVD), microvascular complications, and lower extremity vascular disease (e.g., diabetic foot) complications; meanwhile, it is also believed that T2DM is associated with an increase in cognitive decline and the risk of dementia [2]. Currently, there is an active academic research around T2MD. Recent studies on T2DM have made significant progress in dietary interventions and dietary factors. Several studies have shown that healthy dietary patterns such as the Mediterranean diet and the DASH diet significantly reduce the risk of T2DM, and that a

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high intake of specific food groups such as whole grains and low-fat dairy products is beneficial, whereas unhealthy diets such as high glycemic index diets and red meat increase the risk of developing the disease; and that the combination of dietary and physical activity interventions were effective in preventing T2DM in both high-risk and general populations, as were low-calorie and low-carbohydrate diets [3].

T2DM's incidence has been increasing year by year in recent years, which is causing a significant burden on the healthcare system and socio-economics: from the healthcare system perspective, the large number of diabetic patients and the need for long-term management continue to consume a large amount of healthcare resources, including frequent visits to the hospital for checkups, medication, and management of complications, which aggravates the burden on hospital facilities and healthcare personnel. From a socioeconomic perspective, patients miss work and lose their ability to work due to illness, and family income is damaged, while the high medical costs also put great pressure on the health insurance fund and the social economy. Therefore, an in-depth understanding of the pathophysiologic mechanisms of T2DM and the development of comprehensive management strategies are of great clinical and public health significance.

This article will provide an overview of the epidemiology of T2DM, therapeutic strategies, with a focus on the pathophysiologic basis, genetics, and cell biological mechanisms of T2MD. This article examines the literature related to T2DM in recent years, and through systematic categorization and screening, analyzes the existing research results by over multiple aspects and provides insights into the future of T2DM research. The aim of this paper is to provide researchers with a more comprehensive understanding of T2DM research in the hope of advancing relevant developments in the field. In addition, it is hoped that this paper can accelerate research on T2DM and find more effective treatments.

2. Epidemiology and risk factors of T2DM

2.1. Epidemiological trends and characteristics of T2DM

Common complications of T2DM include hypoglycemia, acute ischemic stroke, and retinopathy, which can lead to severe consequences such as blindness [4]. Randomized controlled trials have shown that T2DM patients experience a range of 0.7 to 12 episodes of severe hypoglycemia per 100 person-years. Observational studies have found that hypoglycemia leads to a range of hospitalizations or emergency department visits, ranging from 0.2 per 100 person-years (untreated) to 2.0 per 100 person-years (treated) [5]. severe hypoglycemia was characterized by significant cognitive impairment, in general, regardless of the blood glucose level, assistance from another person is needed to recover [6]. In acute ischemic stroke, patients with T2DM mellitus (T2DM) have a significantly higher risk of ischemic stroke compared to non-T2DM patients [7].In recent years, there has been a decline in the incidence of most chronic vascular complications of diabetes in developed countries, which could be due to improvements in early diagnosis and treatment of diabetes [8]. The leading cause of visual impairment and blindness worldwide is diabetic retinopathy (DR), which is a common microvascular complication [9]. The incidence of diabetic DR among patients with T2DM is generally lower, as revealed by studies after 2000. The incidence of DR decreased significantly between 2013 and 2016 according to a study in the United Kingdom [10].

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2.2. Modifiable and non-modifiable risk factors for T2DM

The risk factors for T2DM are diverse. T2DM is usually more prevalent among adults. However, in recent years, the incidence rate among young people has been increasing [11]. This may be related to the rising prevalence of obesity and a sedentary lifestyle. The prevalence of T2DM (T2D) is increasing among adolescents, and the incidence varies by geographic region. As an illustration, the occurrence is growing in economically disadvantaged countries. The prevalence of T2DM shows a distribution pattern that correlates with economic development. Dyslipidemia, also known as dyslipidemia, occurs when there is an uncontrolled increase in total cholesterol and triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) in the clinical setting.

3. The pathophysiological basis of T2DM

3.1. IR and beta-cell dysfunction in T2DM

IR is the condition where the body's tissues (such as muscles, fat, and liver) have a diminished response to insulin, resulting in the inability of insulin to effectively promote the uptake and utilization of glucose by cells. This means that the body requires more insulin to achieve normal blood glucose regulation. In T2DM, the elevated levels of glucose in the bloodstream are caused by impaired glucose tolerance, which is a cause of IR. IR is common in the elderly, but it is becoming increasingly prevalent across all age groups, including middle-aged individuals who are overweight and sedentary [12,13].

Beta-cell dysfunction refers to the abnormal functioning of the beta cells (pancreatic beta cells) in the pancreas, which are responsible for secreting insulin. These cells are unable to secrete insulin normally or respond appropriately to changes in blood glucose levels.

3.2. Key molecular mechanisms

The molecular mechanism of T2DM is very complex, mainly including insulin secretion deficiency and IR [14].

Insulin secretion deficiency promotes the occurrence and development of T2DM. This is a possible cause caused by defects in the pathways that regulate insulin signaling, such as insulin receptors, IRS proteins, and PI3K/AKT. Abnormal functions of β cells (reduced number of β cells and abnormal intracellular calcium ion signaling) lead to decreased insulin production; IR and abnormal metabolic states of peripheral tissues both promote the occurrence of these conditions. Lipid toxicity and glucose toxicity damage the function of β cells, β cells are afflicted with oxidative damage and endoplasmic reticulum stress, and ultimately resulting in insulin secretion defects [15].

The efficiency of insulin in regulating blood sugar decreases due to the reduced response ability of insulin-sensitive cells to insulin, which is referred to as IR. IR usually occurs in skeletal muscle, adipose tissue and the liver. Hyperglycemia can be caused by a decline in the body's ability to take up and oxidize glucose due to various insulin signal transduction disorders in patients with T2DM. At the same time, excessive food intake or long-term lack of physical exercise can also affect the process of glucose absorption and conversion by muscle cells, thereby exacerbating IR.

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4. Genetics and epigenetic mechanisms

4.1. Susceptibility genes and polygenic risk assessment

T2DM is a complex genetic disease, which is caused by the combined effect of multiple genes and various environmental factors. Although more than 400 susceptibility loci for T2DM have been identified through large-sample GWAS studies, the proportion of heritability explained does not exceed 20%, indicating that there are still many unknown, rare and more influential pathogenic variations. Secondly, existing evidence indicates that some single-gene mutations such as Hepatocyte Nuclear Factor 1 Alpha and Glucokinase are simultaneously associated with MODY and T2DM, and different results will occur when the degree of functional impairment is different. The causes of this disease should be explored from various aspects such as the genome, epigenome and some environmental factors. In future research, more omics and functional data support is also needed to better improve the precise prevention and treatment of the disease. Using these numerous existing related studies, a predictive model can be constructed to estimate the risk value of T2DM in the population, namely the polygenic risk score (PRS) based on GWAS data [16].

4.2. Environment-gene interactions

The occurrence and development of T2DM is the result of the combined action of genetic factors and environmental factors. In recent years, the importance of environment-gene interaction in the study of T2DM has become increasingly prominent. Studies have shown that individuals with genetic susceptibility are more likely to develop T2DM under the influence of specific environmental factors. Among them, the adiponectin gene is an important gene for the interaction between T2DM and the environment.

Adiponectin is a bioactive protein secreted by adipose tissue, which plays an important role in regulating glycolipid metabolism, improving insulin sensitivity and anti-inflammation. Adiponectin levels are negatively correlated with the degree of IR. The polymorphism of the adiponectin gene (ADIPOQ) may affect an individual's susceptibility to T2DM by influencing the expression and function of adiponectin. Studies have found that multiple single nucleotide polymorphisms (SNPs) of the adiponectin gene, such as rs10937273, rs1501299, rs182052, rs2241767 and rs266729, are significantly associated with the occurrence of T2DM. In particular, there is a significant interaction between these SNPs and central obesity, indicating that adiponectin gene polymorphisms may increase the risk of T2DM by affecting an individual's metabolic status.

Environmental factors such as hypertension, high-calorie diet, nicotine consumption, excessive drinking and physical inactivity have also been found to have significant interactions with the polymorphism of adiponectin genes. For instance, the interaction between rs1501299 and hypertension and a high-fat diet is significant, indicating that these environmental factors may further increase the risk of T2DM in genetically susceptible individuals. Furthermore, central obesity, as an important environmental risk factor, has a significant interaction with multiple adiponectin gene SNPs, adiponectin expression and function may be influenced by obesity, leading to a higher risk of developing T2DM [17].

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5. Cell biology of metabolic disorders

5.1. Adipose tissue dysfunction and inflammation

Adipose tissue dysfunction is one of the important pathological bases of T2DM. Adipose tissue dysfunction refers to the abnormalities in the structure, metabolism or secretion function of adipose tissue, which leads to the impairment of its normal physiological function, and then triggers the state of systemic metabolic disorder. In general, adipose tissue dysfunction is associated with abnormal white adipocytes. These cells enlarge and produce more inflammatory factors as a result of obesity, leading to IR.

On the other hand, systemic inflammation is one of the most important factors contributing to the development of T2DM. Circulating lipopolysaccharide (LPS), hypoxia and fibrosis trigger inflammation and activate the intrinsic immune system, which in turn leads to tissue damage and even fibrosis. This inflammation damages multiple organs, led by the pancreas Prolonged low-grade inflammation leads to reduced beta cell mass and dysfunction, which ultimately triggers T2DM [18].

5.2. Abnormalities of hepatic glucose metabolism

Abnormal hepatic glucose metabolism is a state of dysfunction in the liver during glycogen synthesis, catabolism, gluconeogenesis, or glucose output, resulting in an imbalance in blood glucose regulation. Under normal conditions, insulin maintains glucose homeostasis by activating insulin receptors in the liver to promote glucose uptake and inhibit gluconeogenesis. In T2DM, however, IR usually leads to insensitivity of the liver to insulin signaling, which in turn leads to decreased glycogen synthesis, increased gluconeogenesis, and hepatic disregard of hyperglycemia and exacerbation of hyperglycemia.

Under the state of IR, the insulin signal transduction pathways in the liver are impaired, especially the activities of PI3K/AKT decrease, which weakens the inhibitory effect of insulin on gluconeogenesis. Furthermore, IR is also associated with the abnormal activation of sterol regulatory element-binding proteins (SREBP), which are typically involved in lipid synthesis but may indirectly affect glucose metabolism in T2DM. Due to the disorder of insulin signal transduction, the liver is unable to effectively convert excess glucose into glycogen for storage. Instead, it continuously releases glucose into the bloodstream, further exacerbating the hyperglycemic state [19]. Therefore, understanding the abnormal mechanism of liver insulin signal transduction in T2DM is crucial for developing effective therapeutic strategies.

6. Comprehensive treatment strategies for T2DM

The primary objective of T2DM therapy is to control blood glucose levels by means of lifestyle changes, oral medications, and insulin therapy. The first step in routine treatment is diet and exercise. Included are oral anti-diabetic medicines. These medicines are classified and can be utilized either as a single treatment or in combination with other medicines, such as Biguanides and Insulin Secretagogues.

Several anti-diabetic drugs have been developed in recent years, while others are still under intense research in clinical trials. These new therapies assist in lowering blood glucose levels and addressing the metabolic components that contribute to diabetes. Examples of activin Type II receptor modulators include bimagrumab and amylin or dual amylin-calcitonin receptor agonists such as pramlintide-amylin agonist. The objective of these treatments is to enhance the management

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of diabetes by managing blood glucose levels and addressing the broader metabolic issues that are connected with the condition.

6.1. Lifestyle intervention and basic therapy

The management of T2DM requires non-pharmacological approaches to be of great importance. Where lifestyle changes alone are insufficient to achieve a positive outcome, pharmacological approaches may be included. The use of drug therapy, lifestyle changes, and psychosocial interventions is supported by recent research as a comprehensive and integrated treatment for T2DM.

Non-pharmacological treatment methods include exercise; dietary intervention; bariatric surgery; behavioral and psychological interventions, Cognitive-behavioral therapy (CBT) has been demonstrated to be a successful method for treating diabetes patients; hyperbaric oxygen therapy; and probiotics [20].

6.2. Pharmacological treatment

Canagliflozin is also referred to as. The proximal renal tubule of the kidney is where SGLT2 (Sodium-Glucose cotransporter 2) plays a significant role in glucose reabsorption. The SGLT2 inhibitor (SGLT2i) acts by blocking this protein, which lowers blood glucose levels [21].

Epithelial L cells secrete Glucagon-like peptide (GLP-1) as a response to nutritional intake, particularly glucose and lipids. GLP-1 exerts its effects on multiple organ systems. It is a type of incretin that enhances the release of glucose-dependent insulin from the pancreatic β-cell, promotes the neogenesis of β-cell, inhibits the apoptosis of β-cell, and inhibits the secretion of glucagon from α-cells (as seen in rodent studies） [22].

Following the discovery of GLP-1, DPP-4 inhibition has become the focus of research, Inhibition of DPP-4 significantly enhances the activity of incretin hormones by increasing the level of endogenous active peptides. The primary DPP-4 inhibitory effect is attributable to increased GLP-1 levels. Tirzepatide is a new medicine that makes use of the dual agonism of insulinotropic peptide GLP/GLP-1 receptors to improve blood glucose control and significantly reduce body weight [23].

7. Conclusion

In this paper, we review the epidemiology, pathophysiology, genetics, epigenetic mechanisms and therapeutic strategies of T2DM. On the basis of analyzing the present literature, this paper summarizes the developing tendency of T2DM and identifies the risk factors of T2DM. Furthermore, emphasis was placed on the importance of lifestyle interventions and new therapies (for example, SGLT2 inhibitors, GLP-1 receptor agonists, and novel dual agonist treatments like telesipatin).

This research has important meaning for clinic and public health. The analysis emphasizes the multi-factorial character of T2DM, and the need for an integrated treatment strategy that addresses both metabolic and genetic factors. It is concluded that the early intervention combined with lifestyle change and targeted medication can effectively control and decrease the complications of T2DM. Furthermore, the potential of genetic and epigenetic research to improve individualized therapy strategies was highlighted.

However, there are some limitations in this thesis. Further research is needed on some aspects (for example, long term effects of new treatments and detailed molecular mechanisms of genetic and

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environmental interactions). Further investigations will concentrate on longitudinal data to enhance understanding of T2DM progression and the enduring effects of therapeutic interventions. Furthermore, exploring the role of new technologies, such as AI and omics platforms, could provide new insights into disease forecasting and management. Overall, ongoing research and innovation are crucial for the development of more efficient and personalised T2DM therapies, which will improve patient outcomes and reduce the burden on the healthcare system.

Authors contribution

All the authors contributed equally and their names were listed in alphabetical order.

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