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Complications of Type 2 Diabetes Mellitus and Its Drug Therapy

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Abstract:

Diabetes is common around the world. It has several types and, among them, type 2 diabetes mellitus (T2DM) is very common in many countries and can be found in all age groups. T2DM has some complications that really make patients' lives inconvenient and some of the complications can bring high mortality. This review discusses how these complications happen and drug therapies for some of the diseases, also talks about some other factors that could make drug therapies different and gives some ways to discover drugs that can improve treatment plans. The complications of type 2 diabetes mellitus are mostly micro- or macrovascular diseases, whose onset and progression are caused by its uncontrolled nature. At present, the drug treatment for type 2 diabetes includes two types: oral hypoglycemic drugs and injectable preparations. At present, the treatment of type 2 diabetes focuses on comprehensive management, with the goal of controlling blood sugar and preventing complications. Future research may focus on new drug development, technological and therapeutic innovations, early intervention and reversal of type 2 diabetes.

Keywords: Complications; Type 2 Diabetes Mellitus; Drug Therapy; Pharmacological Interventions

1. Introduction

Diabetes is a common chronic disease worldwide. Since 2000, mortality rates from diabetes have been increasing, while other diseases have shown a tendency to decrease in mortality at the beginning of this century [1]. Among all types of diabetes, type 2 diabetes mellitus (T2DM) is more common in the public because it can be related to obesity. Patients who have T2DM, often have complications. These complications may cause many problems that can lead to death instead of T2DM itself.

T2DM has numerous complications, and some patients find they have T2DM because they have symptoms of complications. Therefore, patients may not only need T2DM drugs but also other drugs to manage these complications. Patients often take several tablets each day, and in real situations, drug therapies for the complications of T2DM are often ignored [2]. Given these situations, this review will introduce

some common complications of T2DM, how they occur, and how to use drugs to treat patients. The review will also discuss the influence of individual differences on treatment outcomes.

2. Classification and Mechanism of Complications of T2DM

2.1 Microvascular Diseases

Retinopathy (damage to the eyes), nephropathy (injury to the kidneys), and neuropathy (issues with the nerve system) are examples of microvascular disorders.

2.1.1 Retinopathy

Retinopathy is one of the most common complications, affecting approximately 35% of all diabetic patients [3]. Hyperglycemia causes prolonged high stress, leading to abnormalities in several microvessels in the eyes. Hyperglycemia can induce the production of reactive oxygen species (ROS), which can lead to oxidative stress, DNA damage, and mitochondrial dysfunction of cells. The retina is highly vulnerable to oxidative stress, and hyperglycemic conditions in T2DM lead to retinal blood vessels losing function. The blood vessels that nourish the retina of the eye are often blocked in T2DM patients; as a result, tiny bulges protrude from the blood vessels, which hinder regular blood supply to the eye, ultimately leading to vision loss, one of the major consequences of diabetic retinopathy [4].

2.1.2 Nephropathy

Diabetic nephropathy is another microvascular disease, often related to hyperglycemia in patients with T2DM. Many cell types in the kidney are affected by diabetic nephropathy, including endothelial cells, renal tubular interstitial cells, podocytes, and mesangial cells. The kidneys play a vital role in glucose homeostasis, contributing about 20%-25% of total body glucose release and 40% of total gluconeogenesis in the body [5].

2.1.3 Neuropathy

Diabetic neuropathy is another severe microvascular complication caused by nerve damage due to impairment of the myelin sheath and Schwann cells, leading to axonal atrophy and apoptosis. Hyperglycemia and insulin resistance used to cause oxidative stress, inflammation, and mitochondrial dysfunction in peripheral nerves. The accumulation of AGEs and the activation of the polyol pathway lead to nerve damage and impaired nerve conduction. The signs of diabetic neuropathy manifest as numbness, prickling sensations, discomfort, and muscular weakness in the limbs. The condition can progress to diabetic foot ulcers and amputation in severe cases [6].

2.2 Macrovascular Diseases

Macrovascular diseases include cardiovascular disease and brain diseases (especially stroke).

2.2.1 Cardiovascular Diseases

Approximately 32% of T2DM patients suffer from cardiovascular diseases, which have high mortality rates [7]. Hyperglycemia, insulin resistance, and dyslipidemia promote the development of atherosclerosis. Elevated levels of triglycerides, low-density lipoprotein (LDL), and reduced high-density lipoprotein (HDL) promote plaque formation and arterial stiffness. Chronic inflammation and endothelial dysfunction further exacerbate cardiovascular risk. Clinical manifestations include pain, numbness, and ulcers in the lower limbs, with an increased risk of amputation in severe cases [8].

2.2.2 Brain Diseases

T2DM has a great impact on the onset and progression of brain disorders or diseases, like stroke, dementia, and depression. Hyperglycemia and insulin resistance contribute to neuroinflammation and oxidative stress, which can lead to cognitive decline and increased risk of stroke [9].

2.3 Other Diseases

Other common complications with T2DM include hepatic diseases and cancer.

2.3.1 Hepatic Diseases

Nonalcoholic fatty liver disease (NAFLD) begins with the accumulation of fat in the liver (hepatic steatosis), which T2DM strongly contributes to the onset of NAFLD. NAFLD can progress to nonalcoholic steatohepatitis (NASH) [10].

2.3.2 Cancer

T2DM increases the risk of cancer in patients. Hyper-

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glycemia, insulin resistance, hyperinsulinemia, elevated levels of insulin-like growth factor-1, and decreased adiponectin, which are factors linked to T2DM, play a role in cancer development [11].

3. Pharmacological Treatment Regimens for Complications of T2DM

3.1 Retinopathy

Intravitreous glucocorticoids are the preferred choice for treating diabetic macular edema. This is because they possess anti-angiogenic and anti-inflammatory properties, which can stabilize the inner blood-retina barrier. Moreover, they are helpful in combating proliferative diabetic retinopathy. Doses ranging from 4 to 25 mg are used. However, this therapy lacks evidence from clinical trials, and there are two disadvantages: the effect lasts only three months, requiring repeated injections, and secondary glaucoma can develop in one-third of patients. Therefore, dexamethasone is used as an alternative treatment [12].

3.2 Macrovascular Diseases

3.2.1 Metformin

Metformin is known for its potential benefits in reducing nonfatal myocardial infarction (MI) risk by 39%. However, observational studies showing reduced cardiovascular (CV) events, CV deaths, and total mortality associated with metformin use are flawed by biases arising from the lack of group matching for all variables that could affect the outcome. Two meta-analyses indicate that controlled trials assessing the efficacy of metformin in patients with type 2 diabetes mellitus (T2DM) did not demonstrate its capacity to alter clinically significant outcomes. Moreover, certain studies reveal that patients receiving a combination of metformin and sulfonylurea have a higher mortality rate than those receiving sulfonylurea alone [13].

3.2.2 GLP-1 Receptor Agonists

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) imitate the action of endogenous GLP-1, leading to glucose-dependent insulin secretion and the suppression of glucagon secretion. The GLP-1 receptor is highly expressed in vascular endothelial cells, smooth muscle cells, and cardiomyocytes, which implies that these medications might have an impact on the whole cardiovascular system. In animal model experiments, it has been demonstrated that GLP-1 RAs can enhance insulin sensitivity, improve left ventricular remodeling, and boost cardiac contractility in models of chronic heart failure (HF) and myocardial infarction (MI). Liraglutide has been found to decrease cardiovascular (CV) events mainly through an anti-atherosclerotic mechanism. Moreover, semaglutide has been shown to substantially reduce the primary composite endpoint of CV death, non-fatal MI, or non-fatal stroke. [14].

3.2.3 Sodium glucose cotransporter 2 (SGLT2) Inhibitors

SGLT2 inhibitors are oral medications used to treat T2DM. They work by inhibiting SGLT2, which is a sodium-glucose cotransporter with low affinity and high capacity and is situated in the proximal tubule. Newly emerging evidence suggests that SGLT2 inhibitors are capable of providing cardioprotection for high-risk patients with T2DM. The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose was the first research to clearly demonstrate the cardiovascular benefits of an SGLT2 inhibitor [15].

4. The Impact of Individual Differences on Complications

4.1 Sex

In microvascular complications, evidence of sex differences is scarce and inconclusive. Men with T2DM show a higher risk of sensory neuropathy, nephropathy, and worse retinal microvascular measures than men with normoglycemia, but this is not seen in women. In macrovascular complications, although the absolute risk of cardiovascular disease (CVD) mortality is higher in men with T2DM, the relative risk (RR) is significantly greater in women with T2DM. CVD risk factors, such as obesity and hypertension, progress during the menopausal transition, it further exacerbates insulin resistance, inflammation, and dyslipidemia in women who have T2DM. Compared to men, women also have a higher relative risk (RR) of heart failure and being hospitalized because of heart failure [16].

4.2 Lifestyle

In the Xin Chai research, lifestyle data is limited, and no significant benefits of risk reduction in CVD were found. In Tatiana Palotta Minari's study, it was found that patients who eat breakfast and do not wake up frequently at midnight may control their glycemia and weight better than those who do not [17].

5. Conclusion

This paper provides an overview of the complications of T2DM and the pharmacological treatments available for these complications. The microvascular complications, including retinopathy, nephropathy, and neuropathy, and macrovascular complications, such as cardiovascular diseases and brain disorders, pose significant challenges to patients' quality of life and mortality. At present, the drug treatment for type 2 diabetes includes two types: oral hypoglycemic drugs and injectable preparations. Metformin (first-line medication, improving insulin resistance), SGLT-2 inhibitors (such as dapagliflozin, protecting the heart and kidneys), DPP-4 inhibitors (such as sitagliptin, reducing the risk of hypoglycemia), sulfonylureas (such as glimepirea, promoting insulin secretion), etc. Insulin (for those with severely elevated blood sugar or whose oral medication has failed) and GLP-1 receptor agonists (such as semaglutide, which has both hypoglycemic and weight-loss effects and protects the heart and kidneys). Current pharmacological treatments, have shown promise in managing these complications. However, individual differences, such as sex and lifestyle, can influence the effectiveness of these treatments.

Future research should focus on new drug development (multiple receptor agonists, new mechanism targets); technological and therapeutic innovations (cell and gene therapy, formulating precise and personalized treatment plans based on genetic testing and metabolic characteristics); early intervention and reversal of type 2 diabetes, etc.

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