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The application of metformin in the treatment of diabetes

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Abstract. In recent years, The Prevalence of Diabetes (TDM) has increased. Metformin, a quintessential hypoglycemic agent, exhibits substantial hypoglycemia effects and possesses various clinical applications. This article reviews the application of metformin in the treatment of diabetes, analyzing its mechanism of action, clinical efficacy, and safety. Studies have found that metformin performs outstandingly in the intervention of pre-diabetes, cardiovascular protection, and weight management, and the combined treatment effects are significant. Its safety and cost-effectiveness make it an irreplaceable position in the treatment of diabetes. Frequent adverse effects of metformin encompass gastrointestinal distress and vitamin B12 deficiency resulting from prolonged usage. The future development of metformin will focus on precision and long-acting effects, optimizing treatment outcomes through targeted and sustained-release technologies, while meeting individual medication needs.

Keywords: metformin, type 2 diabetes mellitus, efficacy evaluation, drug safety

1. Introduction

Diabetes, a worldwide chronic metabolic disorder, has had a persistent increase in prevalence over recent decades. The International Diabetes Federation (IDF) research indicates that the global diabetes patient population has surpassed 400 million and is projected to reach 642 million by 2045 [1]. Diabetes is a chronic metabolic disease that can cause severe harm to multiple systems in the body due to long-term hyperglycemia. For example, it increases the risk of atherosclerosis, leading to myocardial infarction and angina. It also increases the incidence of stroke and diabetic nephropathy. In this context, metformin, a conventional anti-diabetic medication, is extensively utilized in diabetes management owing to its remarkable efficacy and safety profile. This article aims to review the application of metformin in the treatment of diabetes. First, the article looks back at the historical development and classification of metformin, analyzing its advantages and disadvantages in clinical application. Subsequently, it concentrates on examining the clinical utilization of metformin in diabetes management and elucidates its mechanism of action. Finally, this article systematically discusses the adverse reactions of metformin and its personalized treatment plans. This study aims to provide beneficial references for clinical practice and reduce the incidence of diabetes.

2. Overview of metformin

2.1. History and classification

The history of metformin can be traced back to the 1950s. As a biguanide derivative, it was first marketed in France in 1957 for the treatment of diabetes. Compared with early guanidine compounds (such as phenformin), metformin has higher safety and a significantly reduced risk of lactic acidosis. In 1995, the United States Food and Drug Administration (FDA) sanctioned metformin for the management of type 2 diabetes, and it rapidly emerged as a primary hypoglycemic agent globally [2].

Metformin is mainly classified into the following categories based on dosage form and release characteristics:

Ordinary tablets: This is the most common dosage form, usually taken 2-3 times a day. Ordinary tablets dissolve and absorb quickly in the gastrointestinal tract, taking effect quickly, and are suitable for most type 2 diabetes patients.

Sustained-release formulations: Through special processes, the drug is encapsulated in a sustained-release matrix, allowing the drug to be slowly released in the gastrointestinal tract, thereby extending the duration of action. Sustained-release formulations are typically taken once a day, reducing the frequency of dosing and the incidence of gastrointestinal adverse reactions (such as nausea, diarrhea), especially suitable for patients with poor tolerance to ordinary tablets.

Compound formulations: To meet the needs of combination therapy, metformin is often used in combination with other hypoglycemic drugs. Common compound formulations include:

Metformin + DPP-4 inhibitors: Such as sitagliptin/metformin compound tablets, which increase endogenous GLP-1 levels by inhibiting DPP-4 enzyme and enhance insulin secretion.

Metformin + SGLT2 inhibitors: Such as empagliflozin/metformin compound tablets, which increase urinary glucose excretion by inhibiting renal glucose reabsorption.

These classifications not only meet the treatment needs of different patients but also provide more choices for individualized treatment [3].

2.2. Pharmacological characteristics

2.2.1. Chemical structure and properties of metformin

Metformin is a white crystalline powder, chemically designated as 1,1-dimethylbiguanide, with the molecular formula $C_4H_{11}N_5$. The compound has good water solubility, making it suitable for preparation into oral formulations. Metformin has high solubility in water and good chemical stability, facilitating storage and use [4].

After oral administration, metformin is rapidly absorbed, but its absorption rate is not complete, with a bioavailability of about 50%. Food has a minor effect on absorption, and after absorption, the distribution is widespread, but it does not cross the blood-brain barrier. The drug is mainly excreted through the kidneys, with a half-life of about 4-8 hours [5].

2.2.2. Cellular and molecular level mechanism of action

a. Core mechanism

Metformin, as a first-line pharmacotherapy for type 2 diabetes, has undergone substantial investigation about its cellular and molecular mechanisms of action. The core mechanism is the activation of AMP-Activated Protein Kinase (AMPK), an enzyme that plays a key role in cellular energy metabolism. The activation of AMPK is mainly through metformin inhibiting mitochondrial respiratory chain complex I, causing an increase in the intracellular Adenosine Monophosphate/Adenosine triphosphate (AMP/ATP) ratio, thereby activating AMPK [6].

b. AMPK regulation pathways

Activated AMPK modulates energy metabolism via multiple routes, including facilitating the translocation of GLUT4 (Glucose Transporter 4) to the cell membrane, so enhancing glucose uptake in muscle and adipose tissue. Furthermore, AMPK activation suppresses the expression of critical enzymes in hepatic gluconeogenesis, including Glucose-6-Phosphatase (G6Pase) and Phosphoenolpyruvate CarboxyKinase (PEPCK), consequently diminishing hepatic glucose production [7].

c. Non-dependent pathways

In terms of non-dependent pathways, metformin reduces hepatic gluconeogenesis by inhibiting mitochondrial Glycerol-3-Phosphate DeHydrogenase (mGPDH). Moreover, metformin can modulate the intestinal microbiota, enhancing the synthesis of Short-Chain Fatty Acids (SCFAs) in the colon, which subsequently activate G Protein-Coupled Receptors (GPCRs) to augment insulin sensitivity and glucose metabolism [8].

d. Regulation of microRNA (miRNA)

Recent studies have also found that metformin affects the insulin signaling pathway and glucose metabolism by regulating the expression of MicroRNA (miRNA). For example, metformin upregulates the expression of the miR-29 family, thereby inhibiting the expression of insulin resistance-related genes. It is worth noting that this mechanism is still under study, and the specific effects may vary due to individual differences [9].

e. Inhibition of mTOR signaling pathway

Moreover, metformin can impede cell proliferation and tumor growth by obstructing the mTOR (mammalian target of rapamycin) signaling pathway, which holds potential therapeutic relevance for diabetic individuals with cancer. It is worth noting that the application of this mechanism in cancer treatment is still in the research stage [10].

3. The application of metformin in the treatment of diabetes

Overview of the Pathophysiology of Diabetes: Diabetes is a metabolic condition marked by hyperglycemia, with its pathophysiological process involving deficiencies in insulin secretion and/or disorders of insulin action, resulting in disrupted blood glucose homeostasis.

3.1. Monotherapy

3.1.1. Inhibition of hepatic glucose output

Metformin, a fundamental medication for type 2 diabetes, primarily functions by inhibiting hepatic gluconeogenesis, thus diminishing hepatic glucose synthesis. In a healthy condition, the liver synthesizes glucose from non-carbohydrate substrates (including lactate, amino acids, and glycerol) via gluconeogenesis to regulate stable blood glucose levels. In patients with type 2 diabetes, this mechanism is excessively active, resulting in heightened fasting blood glucose levels. Metformin inhibits the activity of mitochondrial complex I in the liver, reducing ATP production, and subsequently activating the AMPK signaling pathway. The activation of AMPK can inhibit the expression of key enzymes in gluconeogenesis (such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase), thereby reducing hepatic glucose production [6,11].

In addition, metformin can also inhibit hepatic glucose output by enhancing hepatic insulin sensitivity. Studies have shown that metformin promotes the phosphorylation of Insulin Receptor Substrate (IRS), thereby enhancing insulin signal transduction. This mechanism not only helps to lower fasting blood glucose but also improves overall blood glucose control. Clinical research data show that after taking metformin, the average fasting blood glucose of overweight patients decreased by 2.2 mmol/L (from 9.3 mmol/L to 7.1 mmol/L), far exceeding the control group's 1.7 mmol/L (from 9.1 mmol/L to 7.4 mmol/L) [11].

3.1.2. Enhancing glucose uptake in muscle and adipose tissue

Another significant effect of metformin is to enhance the ability of muscle and adipose tissue to take up glucose. GLUT4 is an insulin-dependent glucose transporter protein that primarily exists in muscle and adipose tissue. Insulin stimulation induces the translocation of GLUT4 from intracellular vesicles to the cell membrane, facilitating glucose absorption in muscle tissue. This mechanism enhances blood glucose regulation and boosts the efficiency of energy metabolism in the body [12].

Additionally, metformin can improve blood glucose control by regulating the metabolic function of adipose tissue. Studies have shown that metformin can inhibit lipolysis in adipocytes, reducing the release of free fatty acids, thereby lowering peripheral tissue insulin resistance.

3.1.3. Improving insulin sensitivity

Insulin resistance is a fundamental pathophysiological characteristic of type 2 diabetes, marked by reduced sensitivity of peripheral tissues to insulin, resulting in inadequate blood glucose regulation. Clinical studies indicate that metformin therapy can markedly enhance insulin sensitivity in individuals with type 2 diabetes, particularly among those who are overweight or obese. The United Kingdom Prospective Diabetes Study (UKPDS) trial shown that in individuals on metformin, the HOMA-IR index diminished by 23%, while the rate of improvement in metabolic syndrome escalated by 30%. It is evident that metformin treatment can significantly reduce the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index in patients with type 2 diabetes and improve overall blood glucose control [13]. These research findings further confirm the clinical value of metformin in improving insulin sensitivity.

3.1.4. Inhibiting intestinal glucose absorption

The intestine serves as the primary location for glucose absorption, facilitated by Sodium-Glucose Cotransporter 1 (SGLT1) and Glucose Transporter 2 (GLUT2). In patients with type 2 diabetes, the intestine's ability to absorb glucose is enhanced, leading to elevated postprandial blood glucose levels. Metformin reduces intestinal glucose absorption by inhibiting the activity of SGLT1, thereby lowering postprandial blood glucose levels. In addition, metformin can improve the body's metabolic state by regulating the composition and function of gut microbiota, which helps to lower blood glucose levels. These mechanisms further enhance the role of metformin in improving blood glucose control.

3.2. Combination therapy

The combination of metformin with other hypoglycemic drugs (such as insulin, sulfonylureas, etc.) can produce a synergistic hypoglycemic effect. However, it is necessary to pay attention to potential drug interactions, such as an increased risk of hypoglycemia.

3.2.1. Combination with insulin

The combination of metformin with insulin is one of the important strategies for the treatment of Type 2 Diabetes Mellitus (T2DM). This combination can significantly improve blood glucose control while reducing the dosage of insulin and the risk of hypoglycemia. Studies have shown that metformin improves insulin resistance, reduces hepatic glucose production, thereby enhancing the hypoglycemic effect of insulin. In addition, the combination can also alleviate the side effect of weight gain, further improving treatment tolerance.

3.2.2. Combination with other oral hypoglycemic drugs

The combination of metformin with other oral hypoglycemic drugs has also been widely studied. For example, the combination with DPP-4 inhibitors (such as sitagliptin) can lower blood glucose through different mechanisms while reducing the risk of hypoglycemia. Analysis shows that the combination of DPP-4 inhibitors with metformin significantly reduces Glycosylated Hemoglobin (HbA1c) and postprandial blood glucose levels, with good tolerability. Moreover, the conjunction of SGLT2 inhibitors (e.g., dapagliflozin) can further diminish blood glucose levels and enhance insulin sensitivity [14].

4. Discussion

Metformin has a generally high safety profile in clinical use, but there are still some adverse reactions. The most common are gastrointestinal reactions, such as nausea, diarrhea, and abdominal pain, which usually subside with prolonged treatment time. Rare but serious adverse reactions include lactic acidosis, especially in patients with renal insufficiency, which requires caution. Individualized treatment based on genotypes and phenotypes can predict drug efficacy and side effects by detecting gene polymorphisms such as Solute Carrier Family 22 Member 1 Gene (SLC22A1), thereby optimizing dosage. In addition, phenotypic factors such as obesity and the degree of insulin resistance also affect treatment plans. Metformin has synergistic or antagonistic effects with various drugs. For example, the combination with insulin or sulfonylurea drugs can enhance the hypoglycemic effect, but the risk of hypoglycemia must be monitored. In addition, metformin is related to the absorption of vitamin B12, and long-term use may lead to vitamin B12 deficiency.

5. Conclusion

Metformin, as a primary hypoglycemic agent, demonstrates considerable efficacy and safety in diabetic management. Furthermore, the long-term use of metformin has not significantly increased the incidence of adverse reactions, and its tolerance is good, making it suitable for most patients with type 2 diabetes for long-term use. Therefore, the core status of metformin in diabetes treatment is unshakable, and it should be given priority in clinical practice. However, this article does not sufficiently explore the long-term effects and mechanisms of the combination of metformin with other new hypoglycemic drugs. To address these shortcomings, future research can be improved and expanded in the following aspects: first, conducting larger-scale, multicenter, randomized controlled clinical trials, strictly controlling research design and quality, to reduce the impact of heterogeneity on results; second, in-depth study of the combination mechanism of metformin with other new hypoglycemic drugs, exploring more optimized treatment plans; third, combining genomics, metabolomics, and other multi-omics technologies to explore potential targets for individualized treatment, to achieve precision medicine.

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