

## ARTICLE

# Metformin and Lactic Acidosis in Diabetic Patients

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### ABSTRACT

Metformin is the basic drug in the clinical treatment of Diabetes, often used in the treatment of Type 2 Diabetes Mellitus (T2DM). Its effect has been fully verified in the clinical treatment of T2DM. However, in the treatment of T2DM with metformin, there is still a certain probability of related lactic acidosis, and the fatality rate is high. Therefore, is the use of metformin drug treatment a direct risk factor for lactic acidosis in diabetic patients? This paper will review the hypoglycemic mechanism of metformin and related studies on lactic acidosis, so as to further explore the relationship between metformin and lactic acidosis in diabetic patients, and provide help and reference for metformin drugs in the clinical treatment of T2DM.

## 1. Introduction

Metformin is a widely used oral hypoglycemic drugs, have good hypoglycemic effect and the advantages of high safety, strong tolerance, be like the Chinese diabetes society (CDS), Japan diabetes association (JDA), and other academic organizations as type 2 diabetes (T2DM) for the treatment of first-line drugs, at the same time more than academic organization pointed out such as in patients without liver and kidney dysfunction and dose appropriate cases, metformin will always as a treatment of choice for patients with diabetes drug<sup>[1-3]</sup>. However, some studies have shown that taking metformin may be one of the causes of lactic acidosis, with a mortality rate of up to 50%<sup>[4]</sup>.

Correlation lactic Acidosis is the first-line drugs is often accompanied by one of the serious adverse reactions, clinical trials in recent years, studies have shown that doses of Metformin treatment result in the correlation of

lactic Acidosis (MALA) cases are rare, but if the dose is too high, and not considering the circumstances of the body function in patients with abnormal could also lead to plasma lactic acid accumulation, and even cause correlation lactic Acidosis (LA)<sup>[5]</sup>. This article will focus on the mechanism of metformin associated lactic acidosis (MALA) and its related factors to systematically review, in order to further clarify the relationship between the clinical use of metformin and diabetic lactic acidosis.

## 2. Hypoglycemic Mechanism of Metformin

Metformin is often combined with sulfonamide drugs in clinical use, which can effectively reduce blood glucose, and the effect of oral treatment is significant in diabetic patients, and the hypoglycemic effect is confirmed<sup>[6]</sup>. Its hypoglycemic effect mainly includes the following three aspects.

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## 2.1 Inhibition of Glucose Absorption and Promotion of Glucose Utilization

The amount of blood sugar in human body mainly depends on the extent to which glucose is absorbed and utilized by tissues or organs. Glucose is absorbed mainly through the intestines. Glucose absorption by intestinal wall and other tissues is mainly through active transportation and glucose uptake by the carrier and ATP<sup>[7]</sup>. Several recent studies have shown that endotoxin derived from gut microbes may increase the disruption of intestinal barrier function and increase glucose uptake, leading to the development of type 2 diabetes. Some studies have shown that<sup>[8]</sup> metformin can affect the microflora of mice and reduce the abundance of endotoxin-producing mucin-degrading G (-) anaerobes *Akkermansia muciniphila* in the intestinal tract of mice, thereby inhibiting excessive glucose absorption and thereby reducing the incidence of type 2 diabetes<sup>[9, 10]</sup>. Glucose use is regulated mainly by hormones, the most important of which is insulin. Experimental results show that the oral metformin can improve mice to mice pancreas litres of blood sugar hormone kind of peptide 1 (glp-1) content, but its mechanism is still unclear, glp-1 have promote insulin secretion, enhance tissue sensitivity to insulin, alpha cells glucagon secretion inhibition, and by increasing the body's insulin levels, in turn, promote the use of glucose<sup>[11-13]</sup>. Therefore, metformin, on the one hand, can reduce the absorption of glucose in the intestinal wall, and on the other hand, it can promote the utilization of glucose by regulating GLP-1 to increase the level of insulin.

## 2.2 Inhibition of Liver Glucose Output

In the regulation of human blood glucose, the liver plays an extremely important role in maintaining blood glucose balance. It can not only reduce blood glucose concentration through metabolic methods such as liver glycogen synthesis, but also increase blood glucose concentration through liver glycogen decomposition and gluconeogenesis. Metformin reduces liver glucose production primarily by adenosine activated protein kinase (AMPK). Main effect of metformin on the respiratory chain complexes I to block the mitochondrial respiratory chain reducing intracellular ATP production, in turn, activates AMPK, its possible mechanism is: ① After metformin into cells, by influencing the LKB1 / AMPK signalling to reduce the concentration cAMP, promote response element binding protein 2 (CRCT2) phosphorylation, inhibition of sugar dysplasia the expression of related genes, thereby reducing glycogenesis<sup>[14]</sup>. ② AMPK can activate liver deacetylase (SIRT1) and promote the acetylation and

ubiquitination degradation of CRTC2, thereby inhibiting the transcription of genes related to gluconeogenesis<sup>[15]</sup>.

③ Metformin activated AMPK upregulates the expression of orphan nuclear receptor (SHP), which competes for the binding site of CRTC2 and inhibits the formation of transcriptional complexes, thereby inhibiting the expression of glycogenic related genes<sup>[14]</sup>. In addition, metformin can also reduce gluconeogenesis through other pathways, the possible mechanisms of which are as follows: ① Mitochondrial respiratory chain is blocked by acting on respiratory chain complex I and ATP production is reduced, and ATP has allosteric inhibition on key enzymes in glycolysis<sup>[16]</sup>. ② The decrease of ATP is accompanied by the increase of AMP, which inhibits the increase of blood glucose by inhibiting the glucagon signaling pathway<sup>[17]</sup>. ③ Metformin directly inhibits mitochondrial glycerol-3-phosphate dehydrogenase, enhances cytoplasmic reductive state, and inhibits the conversion of glycerol and lactic acid to glucose.

## 2.3 Improve Insulin Sensitivity and Insulin Resistance (IR)

After absorption into blood, metformin can act on organs around the liver, increase the number of insulin receptors and tyrosine kinase activity, and also improve the ability of insulin receptors and insulin binding, so as to improve the responsiveness of tissues and organs around the liver to insulin. Carolina et al. showed that when metformin was applied in clinical treatment, it could increase the insulin responsiveness of tissues and organs around the liver, so as to improve the utilization of glucose by tissue cells guided by hypoglycemic hormone<sup>[18]</sup>. Metformin also increases glucose transporter 4 (GLUT-4) gene expression in skeletal muscle cells, thereby increasing the number and activity of GLUT-4 in skeletal muscle cells, thereby reducing peripheral insulin resistance (IR)<sup>[19]</sup>. In adipose tissue, metformin inhibits the phosphorylation of carbohydrate response element (ChREBP) and sterol binding element -1c (SREBP-1c) through AMPK signaling pathway, promotes the reconversion of free fatty acids (FFA) to triglycerides and inhibits the decomposition of triglycerides. AMPK can also directly reduce acetyl-CoA carboxylase (ACC) activity and  $\beta$ -oxidation, thereby indirectly improving IR<sup>[20]</sup>.

## 3. Metguanidines and Lactic Acidosis

Lactic acidosis is a type of anion gap metabolic acidosis that occurs when lactic acid production is increased or metabolic pathways are blocked. When the disease is severe, it often involves multi-system organ function and

has a high-risk of death <sup>[21-22]</sup>. The hypoglycemic effect of guanidine drugs is mainly realized by inhibiting liver glucose production and glucagon secretion and other mechanisms. It can play a role in lowering blood glucose in diabetic patients with normal or abnormal insulin secretion, but has no significant lowering effect on blood glucose in non-diabetic patients <sup>[23]</sup>. The most common adverse reaction in the treatment of formin drugs is lactic acidosis, and MALA is a rare adverse reaction of metformin with a high fatality rate up to 50% <sup>[24]</sup>, which is caused by the enhanced effect of formin drugs on the metabolism of reducing glucose. Metformin has been recognized as one of the first choice drugs for the treatment of type 2 diabetes due to its superior hypoglycemic effect, good tolerance and high safety. Metformin reduces lactic acid gluconeogenesis, thereby reducing the production of glucose, thereby accumulating lactic acid and thereby increasing the possibility of lactic acidosis in diabetic patients <sup>[4,23,25]</sup>.

In clinical studies, cases of MALA are rare. There have been reports of cases of LA in type 2 diabetic patients taking metformin, but these reports do not have a large number of data to show a clear causal relationship between metformin and lactic acidosis, and medical evidence is lacking. However, a large number of previous meta-analyses have shown that the use of metformin has no significant correlation with the incidence of lactic acidosis and the mortality caused by lactic acidosis <sup>[23]</sup>. Previous studies have shown that MALA patients are often associated with secondary diseases that accelerate metabolic decompensation, usually infection, acute kidney, liver failure, or heart failure <sup>[26-28]</sup>. Although a possible role cannot be ruled out, most researchers agree that metformin does not consistently correlate with the degree of acidosis. It is generally believed that the associated exacerbation of high-risk diseases such as heart, kidney, and respiratory failure is the cause of the high mortality of lactic acidosis rather than the effect of metformin <sup>[29]</sup>. Scale et al. believed that compared with metformin, the organic changes of tissues and organs caused by diabetes itself were more of a risk factor for LA, and the possible mechanism was that microvascular lesions caused by diabetes caused tissue hypoxia, thus increasing the risk of LA <sup>[30]</sup>. However, there are no substantial data showing a clear causal relationship between appropriate doses of metformin and lactic acidosis in patients without liver or kidney impairment.

### 3.1 Factors Influencing Metformin - Associated Lactic Acidosis (MALA)

As mentioned earlier, metaguanides are associated with an increased risk of lactic acidosis in diabetes treatment. However, due to the differences in molecular structure and

chemical properties, metformin does not inhibit the release and metabolism of lactic acid. Therefore, the possibility of LA occurrence caused by metformin is much lower than that of other metformin drugs, and it is a relatively safe drug. According to many clinical studies, the occurrence of LA in the treatment of diabetes with metformin is very rare, and most of the cases are often accompanied by cardiopulmonary insufficiency, renal dysfunction and other diseases. Meanwhile, the incidence of lactic acidosis caused by metformin is also related to age and dosage <sup>[31]</sup>.

### 3.2 Renal Insufficiency and MALA

Metformin is mainly excreted after the formation of water-soluble compounds through the treatment of oxidative reducing water and other processes of the kidney. In general, metformin is mainly excreted through renal tubules, so as to ensure an appropriate level of metformin in the body. Thus, when renal function is normal, clinical treatment with medical doses of metformin does not result in lactic acidosis. When kidney dysfunction occurs, metformin cannot be effectively excreted, leading to metformin deposition in the body, which leads to elevated lactic acid levels in the body. Tian Hui et al. carried out an experiment, selected 243 elderly patients with T2DM, and observed the blood lactic acid level of patients before and after metformin alone, combined with other oral hypoglycemic agents or combined with insulin, and found that there was no statistical significance in the fluctuation of blood lactic acid content in patients, and no lactic acidosis event was observed <sup>[32]</sup>. Our guess is that severe kidney failure leads to a significant increase in lactate levels in the body.

### 3.3 Hypoxia and MALA

#### 3.3.1 Cardiac Insufficiency and MALA

Most clinical studies have shown that the probability of metformin directly causing LA in patients is very small, while the probability of lactic acidosis in an anoxic state is sharply increased <sup>[33]</sup>. Diabetic patients are far more likely to suffer from heart failure than healthy people. If acute heart failure, myocardial infarction and other diseases occur in the body, it will lead to cardiac pumping dysfunction, which will lead to the decline of human circulation function, resulting in hypoxia of tissues and organs and lead to functional disorders. Therefore, the ability of important organs such as liver and kidney to remove lactic acid may decrease, and the lactic acid content may be affected and tends to rise, and even lactic acidosis may occur in the human body. Moreover, due to the increase of lactic acid accumulation, the K<sup>+</sup> channel of cardiomyo-

cytes is stimulated to expand and the K<sup>+</sup> outflow degree is increased. The adverse effect is inhibited on the Ca<sup>+</sup> channel, resulting in the decrease of cellular ion concentration, and then the weakening of cardiac systolic function, forming a chain of adverse reactions<sup>[34-35]</sup>.

Therefore, metformin is often contraindicated for heart failure patients in clinical practice. Studies the selection of diabetes patients with heart failure in 1997-2006 (n = 10920), these patients through the use of metformin or sulfonylureas fall blood sugar, such as drug therapy, patients at the same time of voluntary participation in research study until the end of 2006, finally found a total of 6, 187 (57%) patients died, the process and no lactic acidosis patients in experimental<sup>[36]</sup>. Evans et al., Roussel et al., also reached the same conclusion in the same year<sup>[37,38]</sup>. Relevant literature has shown that metformin plays a certain role in antioxidant protection of cardiovascular disease<sup>[39]</sup>. Therefore, when the body does not have hypoxia caused by acute cardiac dysfunction, metformin can be used in patients with diabetes and cardiac dysfunction, but follow-up experimental studies are still needed to verify this.

### 3.3.2 Alcohol Intake and MALA

Long-term alcohol intake may lead to liver damage and even terminal liver disease. Liver is the main place for lactic acid metabolism, and metformin also causes the increase of lactic acid by inhibiting the metabolism of lactic acid in the liver. Therefore, in the case of liver injury, the use of metformin will lead to the increase of lactic acid content in the body, leading to lactic acidosis. Krzymień, etc, according to a study in 29 patients with correlation lactic acidosis (8 cases of metformin treatment, 21 cases of other glucose-lowering drugs or treatment), 12 cases of alcoholic patients, 5 cases of death cases, 3 cases of metformin treatment, therefore the literature suggests that patients with diabetes with correlation of lactic acidosis with metformin use has no obvious relation, and with greater<sup>[40]</sup> the correlation of alcohol abuse. The specific mechanism is that alcohol stimulates the intestinal wall and produces a large amount of lactic acid accumulation, which needs to be transformed with the help of the liver. If the patient is alcoholized and the lesion involves the liver, ethanol metabolism in the liver cells has a synergistic effect with the conversion of pyruvate to lactic acid, and it can also inhibit the degree of glycoeogenesis of pyruvate. Therefore, chronic alcoholism may impair liver parenchyma, thereby attenuate hepatic gluconeogenesis. Metformin has a similar effect to alcoholism, both promoting lactic acid production and preventing lactic acid metabolism<sup>[41]</sup>. They work in synergy. Therefore, heavy alcohol intake

and chronic alcoholism may increase the incidence of MALA.

### 3.4 Age and MALA

With the increase of age, the liver and kidney functions of the elderly gradually decrease; meanwhile, the long-term lesions of the microvessels in the elderly diabetic patients tend to cause hypoxia in the surrounding tissues, resulting in the increase of metformin and lactic acid content, which eventually leads to lactic acid accumulation and poisoning<sup>[33]</sup>. Based on the data analysis of 12 diabetic patients with lactic acidosis caused by clinical treatment with metformin by Hua Zhong et al., it was shown that MALA was mainly characterized by older age, more liver and kidney insufficiency, irregular medication, etc<sup>[42,43]</sup>. Again, age was strongly associated with the incidence of MALA. Therefore, in the treatment of elderly diabetic patients, patients with serious liver and kidney dysfunction should be careful to take biguanidine drugs.

## 4. Summary and Prospect

A rare lactic acidosis occurs during the use of metformin. Is it metformin that is the culprit? Comb through the literature at home and abroad were reviewed, found that most of the research results show that has no direct correlation between metformin and lactic acidosis, at the same time a large number of clinical randomized controlled support metformin, there is no direct causal relationship between lactic acidosis and<sup>[44-45]</sup>, but the real relationship also need to develop a large number of clinical trials conducted in-depth research for them. What's more, metformin can significantly increase the incidence of lactic acidosis when used in patients with liver and kidney insufficiency and heart failure. Although the incidence of lactic acidosis is very low, the characteristics of high mortality still need to be paid attention to by clinical workers. Therefore, patients' conditions, risk factors and physical conditions should be fully evaluated before the use of metformin in the treatment of patients, in order to effectively reduce the adverse reactions of metformin in the clinical treatment of diabetes, including metformin associated lactic acidosis (MALA).

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