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Metformin: An overview

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Abstract

Metformin is a widely prescribed medication for managing type 2 diabetes mellitus, a chronic condition characterized by high blood sugar levels. It belongs to the biguanide class of drugs and is often considered a first-line treatment due to its effectiveness, safety profile, and relatively low cost.The primary mechanism of metformin involves reducing glucose production in the liver while increasing insulin sensitivity in peripheral tissues, such as muscles and fat cells. This results in better glucose utilization by the body, leading to lower blood sugar levels. Additionally, metformin may also have some modest effects on reducing appetite and promoting weight loss, making it beneficial for overweight or obese individuals with diabetes.Beyondits role in diabetes management, metformin has gained attention for its potential benefits in other health conditions. Some research suggests that it may have anti-inflammatory and anti-cancer properties, although further studies are needed to confirm these effects.While metformin is generally well-tolerated, it can cause gastrointestinal side effects such as nausea, diarrhea, and abdominal discomfort, particularly when starting treatment or with higher doses. In rare cases, it may also lead to a serious condition called lactic acidosis, especially in individuals with kidney or liver impairment.

Metformin is usually taken orally in tablet form, typically one to three times daily with meals. Dosage may vary depending on individual factors such as kidney function, age, and other medical conditions. It's important for patients to regularly monitor their blood sugar levels and adhere to their prescribed treatment regimen while taking metformin.Overall, metformin remains a cornerstone in the management of type 2 diabetes and continues to be a subject of research for its potential benefits beyond glycemic control.

Keywords: Diabetes mellitus; Metformin; Lactic acidosis; Weight loss; Polycystic ovary syndrome

1. Introduction

Insulin resistance plays a significant role in the development of cardiovascular disease in individuals with the metabolic syndrome and type 2 diabetes mellitus. Hence, the use of an insulin-sensitizing agent like metformin in patients with type 2 diabetes mellitus can address several primary pathophysiological abnormalities associated with the metabolic syndrome. In diabetic patients, metformin not only helps in controlling blood sugar levels but also offers cardiovascular protection. This protection is not solely attributed to its antihyperglycemic effects. Metformin's additional cardioprotective effects in these patients may be attributed to its positive impact on lipid metabolism, vascular smooth-muscle and cardiomyocyte intracellular calcium handling, endothelial function, hypercoagulation, and platelet hyperactivity. We explore the known mechanisms through which metformin exerts its beneficial effects on glycemic control and cardiovascular health.

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2. Clinical role of metformin

Insulin-resistant individuals who are being treated with metformin may experience additional cardiovascular benefits [1,2,3,4,5]. The weight loss observed during metformin treatment is believed to be a result of reduced caloric intake [6,7,15], likely due to appetite suppression. This effect is not primarily influenced by the gastrointestinal side effects of metformin, such as nausea and diarrhea [10]. The reduction in hyperinsulinemia, which is associated with decreased insulin resistance, may further contribute to weight reduction in obese individuals with insulin resistance [13, 14].Metformin has an oral bioavailability of 50% to 60% when administered at doses ranging from 500 to 1500 mg [16]. It is not bound to proteins and therefore has a large volume of distribution [8], with the highest concentration found in the wall of the small intestine [17]. Metformin does not undergo any changes within the body and is excreted unchanged through the kidneys via rapid elimination (through glomerular filtration and possibly tubular secretion) [8]. Impaired kidney function can slow down the elimination process and lead to metformin accumulation [18]. The H_2-blocker cimetidine competitively inhibits the renal tubular secretion of metformin, resulting in a significant decrease in its clearance and an increase in its bioavailability [16, 19].

3. Metformin as a part of combination therapy

Metformin has demonstrated efficacy when used in combination with insulin, sulfonylureas[1,2,10,20,21], and thiazolidinediones[22]. This is a significant finding as monotherapy often proves insufficient in maintaining normal blood sugar levels, especially as diabetes advances[23,24]. For instance, the UK Prospective Diabetes Study revealed that only 50% of patients achieved the target hemoglobin A1c value of less than 7% after 3 years of treatment with either diet or a single antidiabetic drug. Moreover, after 9 years, only 25% were able to maintain this target. As diabetes progresses and maximum doses of sulfonylureas become ineffective, the addition of metformin has been shown to greatly enhance glycemic control. In fact, in the UKPDS trial, combination therapy was more effective in controlling blood sugar levels compared to monotherapy.

4. Practical consideration in metformin therapy

The ideal candidate to start metformin treatment would be an overweight individual with type 2 diabetes who has normal kidney function. It is important to note that normal kidney function is defined as a creatinine concentration of less than 133 μm d/L in men and less than 124 μm d/L in women, or a creatinine clearance greater than 1.17 ml/s without any coexisting symptomatic congestive heart failure or respiratory conditions[9,16,17,18,25]. It is crucial to consider contraindications to metformin therapy, such as liver failure, alcoholism, and active moderate to severe infections. These conditions can increase the risk of developing lactic acidosis due to either increased production or decreased metabolism of lactic acid. Additionally, the administration of radiocontrast material or general anesthesia can have adverse effects on kidney function and lead to the accumulation of metformin, potentially resulting in toxic levels of the drug. Therefore, if a patient with diabetes requires radiocontrast material or urgent surgery, it is recommended to withhold metformin and ensure proper hydration until kidney function is confirmed to be preserved at 24 and 48 hours after the procedure[26,27,28]. It is also important to exercise caution when prescribing metformin to elderly patients, as their reduced lean body mass may result in misleadingly low creatinine concentrations that do not accurately reflect decreased glomerular filtration rates.

Metformin treatment should start with a single dose of medication, typically 500 mg, taken with the patient's largest meal to prevent gastrointestinal issues[2,8,10,11]. These symptoms usually disappear within 2 weeks of starting treatment[29,30]. The medication dosage can be increased by 500 mg every 1 to 2 weeks based on blood sugar control until reaching the desired blood glucose level or the maximum daily dose of 2550 mg. The hypoglycemic effect of metformin is dose-dependent, with the maximum effect seen at a daily dose of 2000 mg. Side effects are mainly related to the digestive system, such as diarrhea, flatulence, and abdominal discomfort. These symptoms can be managed by gradually increasing the dose and, in some cases, reducing it. Approximately 5% of patients may not tolerate the treatment due to gastrointestinal side effects. The exact mechanisms behind these side effects are not fully understood but may be linked to the accumulation of metformin in the intestinal tissue. Long-term use of metformin can lead to vitamin B12 malabsorption in 10% to 30% of patients[31].

Metformin disrupts the absorption of vitamin B1 in the ileum by interfering with the intracellular calcium handling of mucosal cells [30]. However, this decrease in vitamin B12 levels rarely has any clinical significance [2, 9].The development of hypoglycemia during metformin monotherapy is uncommon because metformin only partially suppresses gluconeogenesis in the liver and does not stimulate insulin production [9, 31]. Lactic acidosis, a life-threatening complication of biguanide therapy, has a mortality rate of 30% to 50% [28]. Metformin therapy can increase

blood lactate levels [1] and is sometimes associated with the development of lactic acidosis [2, 28]. The estimated incidence of metformin-associated lactic acidosis is 0.03 cases per 1000 patient-years [25], which is significantly lower than that observed with phenformin therapy [28]. The development of lactic acidosis does not seem to be related to plasma metformin concentrations [28], and even in individuals with chronic renal insufficiency, metformin accumulation does not necessarily lead to lactic acidosis [18]. The occurrence of lactic acidosis is usually associated with coexisting hypoxic conditions, which likely contribute to the high mortality rate. In one study, 91% of patients who developed lactic acidosis while on metformin treatment had a predisposing condition such as congestive heart failure, renal insufficiency, chronic lung disease with hypoxia, or being over 80 years old [26]. Therefore, metformin should not be given to patients with compromised renal function or coexisting hypoxic conditions. It is important to obtain a detailed history of alcohol use before initiating metformin therapy, as chronic or acute intake of large amounts of alcohol may enhance the effect of metformin on lactate metabolism [26, 27].

5. Mechanism of antihyperglycemic action of metformin

The primary way in which metformin works to lower blood glucose levels is by reducing the amount of glucose produced by the liver. It does this by inhibiting the processes of gluconeogenesis and, to a lesser extent, glycogenolysis. Additionally, metformin increases the uptake of glucose by skeletal muscle and adipocytes in response to insulin. This combined action helps to lower blood glucose levels in individuals with type 2 diabetes. Studies have shown that metformin can decrease fasting plasma glucose concentrations by 25% to 30% and reduce glucose production. These findings are consistent with both in vivo and in vitro studies that have demonstrated the inhibitory effect of metformin on gluconeogenesis.

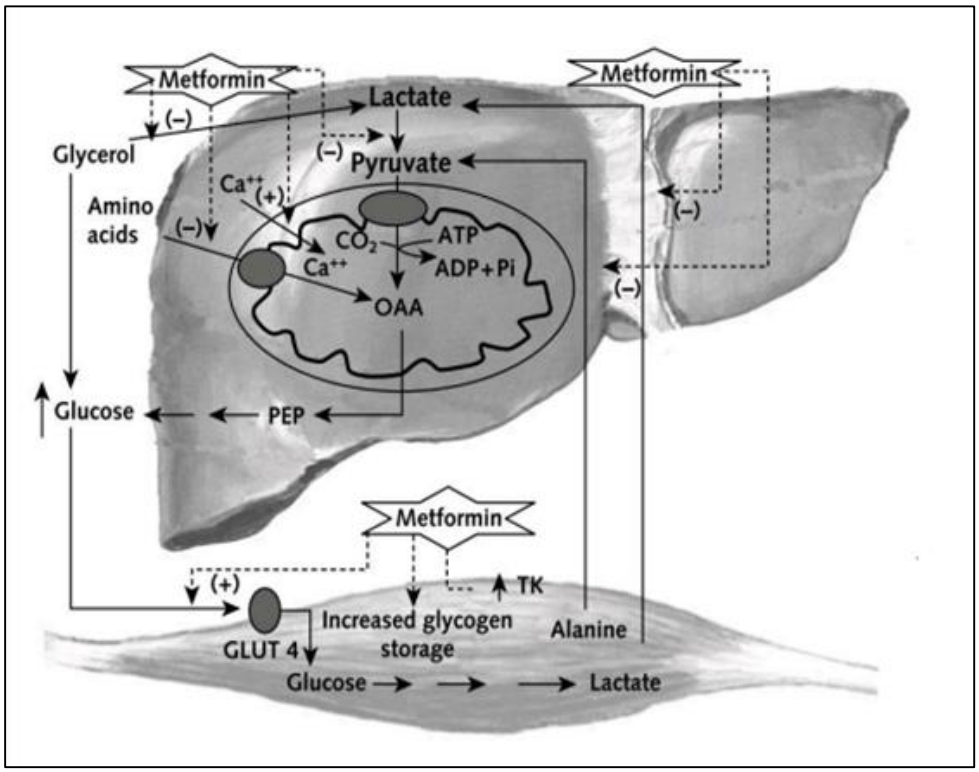

Figure1 Mechanism of metformin action on hepatic glucose production and muscle glucose consumption

Metformin has been observed to reduce gluconeogenesis in the perfused liver by primarily inhibiting hepatic lactate uptake [37]. Other studies have reported that metformin therapy decreases adenosine triphosphate concentrations in isolated rat hepatocytes [38]. The researchers suggested that the metformin-induced decrease in hepatic glucose production may be due to an increase in pyruvate kinase flux, as adenosine triphosphate is an allosteric inhibitor of pyruvate kinase. Additionally, metformin inhibits pyruvate carboxylase-phosphoenolpyruvate carboxykinase activity, leading to a decrease in gluconeogenic flux. It may also increase the conversion of pyruvate to alanine [34]. Furthermore, metformin enhances insulin-induced suppression of gluconeogenesis from various substances such as lactate, pyruvate, glycerol, and amino acids [31]. It also counteracts the gluconeogenic effects of glucagon [39].

The precise mechanism by which metformin reduces hepatic glucose production is still not fully understood. However, it is believed that its main target is the mitochondria within hepatocytes. Metformin disrupts the oxidation of complex 1 substrates, such as glutamate, in the respiratory chain of the mitochondria. This disruption of cellular respiration leads to a decrease in gluconeogenesis and potentially an increase in the expression of glucose transporters, thereby enhancing glucose utilization.

The exact way in which metformin affects mitochondrial respiration is not clear. It is speculated that it may directly act on mitochondrial respiration by slowly permeating across the inner mitochondrial membrane. Alternatively, it may utilize unidentified cell-signaling pathways to exert its effects.

Studies have suggested that biguanides, the class of drugs to which metformin belongs, bind specifically and competitively to divalent cation sites on proteins. This interference with intracellular handling of calcium, especially within the mitochondria, may contribute to the overall effects of metformin.

Research conducted by Davidoff and colleagues demonstrated that even small doses of biguanides can increase the rates of calcium uptake in isolated hepatic mitochondria. Calcium serves as a potent activator of mitochondrial respiration. This effect was observed at concentrations of biguanides as low as 5 to 10 μm, which are expected to be present in the liver when using antihyperglycemic doses of the drug. These concentrations are 20- to 50-fold lower than those required to inhibit mitochondrial respiration.

In addition to its effects on hepatic glucose production, metformin has been shown to facilitate the trafficking of glucose transporters 4 and 1 to the plasma membrane in various tissues, including skeletal muscle and adipocytes. Furthermore, metformin may enhance the glucose transport capacity of glucose transporter 4, and to a lesser extent, glucose transporter 1.

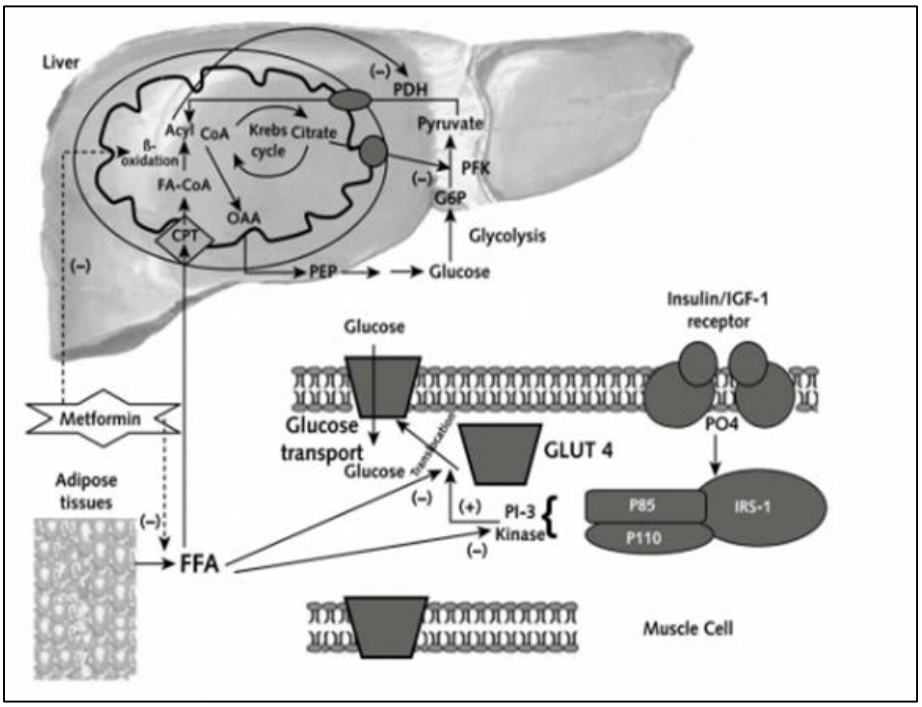

Figure 2 Metformin and fatty acid

Insulin is required for the full action of metformin on peripheral insulin-sensitive tissues. Metformin enhances various biological actions of insulin, such as glucose transport and glycogen and lipid synthesis, particularly in individuals with preexisting insulin resistance. It even promotes glucose transport in skeletal muscle cells without the presence of insulin. Additionally, metformin activates insulin and tyrosine kinase activity in the insulin-like growth factor-1 receptor of vascular smooth-muscle cells independently of insulin action. This activation leads to the production of inositol 1,4,5-triphosphate and glycogen synthesis[1,3,4,5]. These metabolic effects of metformin on insulin-sensitive tissues contribute to its ability to lower glucose levels[2,6,7].

Metformin has also been found to reduce the oxidation of free fatty acids by 10% to 30%. Elevated levels of free fatty acids are commonly observed in individuals with diabetes and obesity, and they contribute to increased hepatic glucose production and the development of insulin resistance. The increased oxidation of fatty acids inhibits key enzymes in the glycolytic pathway due to the accumulation of acetyl coenzyme A and citrate, by-products of fatty acid oxidation. This, in turn, leads to increased concentrations of glucose 6-phosphate, which inhibits the hexokinase enzyme responsible for glucose uptake and oxidation. Furthermore, free fatty acids independently inhibit insulin receptor substrate-1-associated P13-kinase activity and subsequently hinder transmembrane glucose transport. By reducing free fatty acid levels, metformin not only improves insulin sensitivity but also helps correct impaired insulin secretion by B-cells. Although metformin does not directly affect B-cell function, it can enhance insulin secretion that has been compromised by long-term exposure to free fatty acids or hyperglycemia (glucose toxicity).

Metformin has the potential to enhance hyperglycemia by accumulating high concentrations in the small intestine [17, 31] and reducing the absorption of glucose in the intestines [29, 54]. This action may contribute to the reduction of postprandial blood glucose levels [55]. It has been suggested that the increased consumption of glucose in the small intestine of patients treated with metformin may hinder the transportation of glucose to the liver [29].

To summarize, metformin reduces the production of glucose in the liver by inhibiting gluconeogenesis and possibly glycogenolysis. It also improves the sensitivity of peripheral insulin. Furthermore, metformin decreases the absorption of glucose in the gastrointestinal tract and indirectly enhances the response of pancreatic B-cells to glucose by lowering glucose toxicity and levels of free fatty acids.

6. The impact of metformin on polycystic ovary syndrome

Insulin resistance, characterized by hyperinsulinemia, is a common characteristic observed in both lean and obese individuals with polycystic ovary syndrome (PCOS) [11, 56, 57]. This hyperinsulinemia directly contributes to the excessive production of testosterone by the ovaries [56] and a decrease in the synthesis of sex hormone-binding globulin in the liver [11, 41,42,43,58], resulting in elevated levels of total and free testosterone. Metformin therapy has been shown to enhance insulin sensitivity and reduce insulin levels in patients with PCOS [56, 57, 59]. The improvement in hyperinsulinemia is associated with a decrease in total and free testosterone levels [11, 12, 57, 59] and an increase in estradiol levels [12]. From a clinical perspective, the administration of metformin has been found to improve hirsutism [11], normalize menstrual cycles [11, 12, 57, 59,60], and induce ovulation [57, 59] in a significant number of PCOS patients.

7. Effect of metformin treatment on cardiovascular morbidity and mortality

In the UKPDS 34 trial, metformin therapy was compared to conventional treatment involving sulfonylurea or insulin [5]. The study aimed to achieve fasting plasma glucose levels below 6 mmol/L (<108 mg/dL) by assigning 342 newly diagnosed type 2 diabetes patients to the metformin group and 951 patients to receive chlorpropamide, glibenclamide, or insulin. The control group consisted of 411 overweight diabetic patients who were randomly assigned to conventional therapy, mainly through diet alone, resulting in inadequate glycemic control. Over a 10-year follow-up period, both drug-treated groups showed similar levels of glycemic control (median hemoglobin A1c value of 0.074 [7.4%]), while the conventionally treated group had a median hemoglobin A1c value of 0.08 (8.0%) [5,71,72,27,74,75]. Metformin-treated patients had a 32% reduced risk of any diabetes-related endpoint and a 39% lower risk of myocardial infarction compared to the conventionally treated group.42% of diabetes-related deaths and 36% of all-cause mortality can be attributed to differences in glycemic control between the metformin and diet groups [5,76,77,78,79,80]. The UKPDS 35 [60,81,82,83,84,85] found that the risk of cardiovascular events, stroke, and all-cause death was closely linked to glycemia levels in diabetic patients. For every 19% decrease in hemoglobin A1c during treatment for type 2 diabetes, there was a corresponding reduction of 21% in diabetes-related deaths, 14% in myocardial infarction incidence, 12% in fatal and nonfatal strokes, and 16% in heart failure [60]. Despite both agents equally lowering hemoglobin A1c levels, metformin was more effective than sulfonylureas or insulin in reducing rates of diabetes-related endpoints, all-cause mortality, and stroke [5]. These findings suggest that metformin may have additional cardiovascular protective effects beyond its antihyperglycemic properties. However, data indicate that combining metformin with sulfonylurea may increase cardiovascular mortality in patients with type 2 diabetes [5, 61,62,63]. It is important to note that in these studies, metformin was not used as an initial therapy but added when sulfonylurea treatment failed. Patients on combination therapy with metformin and sulfonylurea often had long-standing poorly controlled diabetes and higher obesity rates [61], which could independently contribute to mortality. Therefore, the reported increase in cardiovascular disease risk in patients on combination therapy may be due to

selection bias related to the natural history of long-standing diabetes rather than adverse effects of the combination [62].

8. Mechanism of the cardioprotective action of metformin

Insulin resistance, a fundamental aspect of type 2 diabetes and the metabolic cardiovascular syndrome, is commonly linked with hypertension, abdominal obesity, atherogenic dyslipidemia, and vascular dysfunction, all of which significantly contribute to the acceleration of atherosclerosis [63]. Hyperinsulinemia is a reflection of insulin resistance and may serve as an independent risk factor for coronary artery disease [64-66]. Metformin, an insulin-sensitizing agent, reduces insulin resistance in both diabetic [20, 31, 51,52,53] and non-diabetic [11, 12, 57, 67] patients, thereby effectively lowering baseline and glucose-stimulated insulin levels [12, 20, 55, 57, 67].

Numerous studies have demonstrated that metformin enhances lipoprotein profiles in diabetic individuals [2, 10, 20, 55, 68,69,70]. Dyslipidemia in diabetes is characterized by hypertriglyceridemia (elevated levels of very low-density lipoprotein cholesterol), reduced levels of high-density lipoprotein cholesterol, and increased levels of small, dense atherogenic low-density lipoprotein cholesterol (LDL) particles. The elevated levels of free fatty acids observed in obesity also play a role in this process.

Poorly managed diabetes not only leads to the development of insulin resistance but also results in increased synthesis and secretion of very low-density lipoprotein. Elevated triglyceride levels hinder the breakdown of apoptotein B in the liver, leading to the enhanced formation of very low-density lipoprotein and smaller, denser LDL particles. The excessive production of reactive oxygen species and free radicals by cardiovascular tissue, along with heightened nonenzymatic glycation of lipoproteins, results in the creation of atypical glycooxidized LDL particles. These particles do not bind well to classic LDL receptors but exhibit a strong affinity for "scavenger" receptors, primarily found on macrophages. The accumulation of glycooxidized small, dense LDL particles transforms macrophages into foam cells, crucial in the initial stages of atherosclerotic plaque development. Diabetic individuals have a significantly higher risk of cardiovascular disease compared to the general population, regardless of their cholesterol levels, indicating a more severe form of dyslipidemia. Lowering cholesterol and triglyceride levels has been proven to be particularly beneficial for diabetic patients. Additionally, hypertriglyceridemia may independently increase the risk of cardiovascular disease in individuals with type 2 diabetes. Metformin plays a significant role in lipid metabolism among patients with insulin resistance, reducing plasma levels of free fatty acids and their tissue oxidation, as well as lowering triglycerides and very low-density lipoprotein levels. Metformin therapy also decreases total cholesterol and LDL cholesterol levels while maintaining or even increasing high-density lipoprotein cholesterol levels[44,45,46,47,48,49,50].

Metformin has demonstrated the ability to reduce hypercoagulation and enhance fibrinolysis in insulin-resistant conditions by lowering plasminogen activator inhibitor-1 levels and increasing tissue plasminogen activator activity. Treatment with metformin also diminishes thrombotic tendencies by reducing tissue plasminogen activator antigen and von Willebrand factor levels. In a study involving 457 non-diabetic patients with visceral obesity, metformin was found to be more effective in decreasing von Willebrand factor levels compared to diet therapy. Additionally, metformin therapy resulted in decreased platelet aggregation in diabetic patients[86,87,88,89,90].

9. Metformin and diabetic cardiomyopathy

Metformin is a medication commonly used to treat diabetes. It has been found that individuals with diabetes often have a higher risk of developing congestive heart failure due to various changes in the heart muscle[80]. One specific condition associated with diabetes is diabetic cardiomyopathy, which is characterized by structural changes in the heart muscle and functional abnormalities in relaxation and compliance of the ventricles[81,82,83,84].In diabetic cardiomyopathy, there is delayed relaxation of the heart during diastole, which is the resting phase of the cardiac cycle. This is caused by reduced removal of calcium from the heart muscle cells after contraction. Hyperglycemia, or high blood sugar levels, has been shown to contribute to these functional changes, as well as insulin resistance. However, studies have shown that treatment with metformin can help correct these cardiac abnormalities in animal models of diabetes. Metformin may work by increasing the removal of calcium from the heart muscle cells after contraction, possibly through activation of tyrosine kinase. Importantly, this beneficial effect of metformin on the heart appears to be independent of its insulin-sensitizing properties[85,86].Additionally, metformin has been found to have a sympathoinhibitory effect, meaning it can decrease heart rate in hypertensive rats. This suggests that metformin may have additional cardiovascular benefits beyond its glucose-lowering effects. Despite these promising findings, there have been no clinical trials conducted to investigate the impact of metformin on the development and progression of

congestive heart failure in diabetic patients. Further research is needed to determine the potential role of metformin in managing this condition[87,88].

10. Metformin and vascular reactivity

Insulin plays a crucial role in the regulation of di valent cations in vascular smooth muscle. This function is disrupted in cases of insulin resistance[89,90,91]. The impaired action of insulin in blood vessels can lead to reduced nitric oxide-dependent vascular relaxation, lower sodium pump activity, and elevated levels of calcium in vascular smooth muscle among individuals with type 2 diabetes[92,93,94,95]. These abnormalities in di valent cation and nitric oxide metabolism contribute to the increased vascular resistance and impaired vasorelaxation seen in hypertension, a common condition in diabetic patients. Studies have shown that metformin has antihypertensive effects in both animals and humans. The mechanisms behind metformin's antihypertensive action are intricate and involve both insulin-dependent and insulin-independent vasodilatory effects. For instance, metformin administration in rat tail arteries has been found to enhance repolarization and induce artery relaxation by reducing the increase in intracellular calcium levels in vascular smooth muscle. This reduction in calcium responses may be due to the increased production of nitric oxide by vascular smooth muscle when exposed to metformin[96,97,98]. Nitric oxide has been shown to decrease calcium responses in vascular smooth muscle to vasoconstrictor agents by activating the cyclic guanosine monophosphate pathway[46]. Additionally, metformin may also lower intracellular calcium levels.

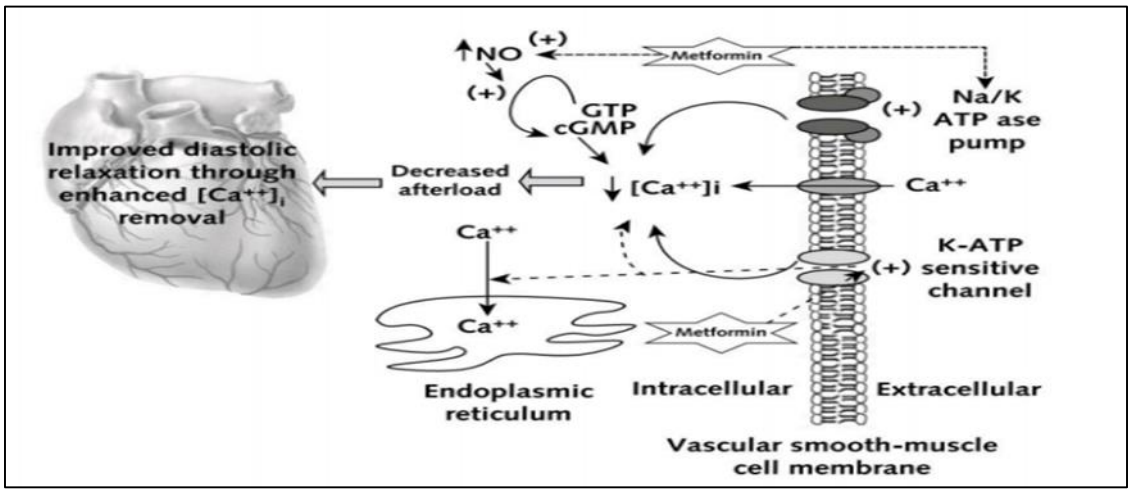

Figure 3 Proposed cellular mechanisms of meformin actionin the vascular smooth muscle cell and cardiomocytes

By enhancing the activity of the sodium adenosine triphosphate pump (99) and promoting the function of adenosine triphosphate sensitive K channels (100) (Figure 3), the effectiveness of metformin in stimulating sodium pump activity is likely associated with increased lactate production in vascular smooth muscle (99, 101). Metformin may exert central antihypertensive effects, as evidenced by the dose-dependent reduction in mean arterial pressure, heart rate, and renal sympathetic nerve activity observed upon infusion of this drug into the lateral cerebral ventricles of spontaneous hypertensive rats (88).

It is important to note that even a slight elevation in blood pressure significantly raises the risk of cardiovascular disease, myocardial infarction, stroke, and congestive heart failure in individuals with diabetes (102). Each 10-mm Hg increase in systolic blood pressure leads to a 15% increase in diabetes-related death rate, an 11% increase in myocardial infarction incidence, a 19% increase in stroke occurrence, and a 12% increase in congestive heart failure (101). Therefore, even a modest reduction in blood pressure during metformin treatment may contribute to a substantial decrease in morbidity and mortality associated with diabetes.

11. Result

Metformin is a widely used medication for managing type 2 diabetes and other conditions such as PCOS. It effectively lowers blood glucose levels by decreasing hepatic glucose production and improving insulin sensitivity. Overall, it's considered safe and well-tolerated, with gastrointestinal side effects being the most common. Recent research also suggests potential benefits beyond glycemic control, such as reducing cardiovascular risk and possibly even extending

lifespan. However, further studies are needed to fully understand its long-term effects and explore its potential in other health conditions.

12. Discussion

The review discusses the effectiveness of metformin in managing type 2 diabetes and other conditions such as PCOS. It may summarize findings from clinical trials and observational studies regarding its ability to lower blood glucose levels, improve insulin sensitivity, and reduce hemoglobin A1c levels.

The safety profile of metformin is examined, including its common side effects such as gastrointestinal disturbances (e.g., diarrhea, nausea, abdominal discomfort) and less common adverse effects like lactic acidosis. The review may also discuss factors influencing the risk of adverse effects, such as dosage and patient characteristics.The mechanisms through which metformin exerts its therapeutic effects are explored. This typically involves its actions on hepatic glucose production, peripheral glucose uptake, and insulin sensitivity, as well as its potential impact on cellular metabolism and signaling pathways.

The review provides guidance on dosage regimens for metformin, including initial dosing, titration strategies, and maximum recommended doses. It may also discuss special considerations for specific patient populations, such as elderly individuals or those with renal impairment.

Beyond type 2 diabetes, the review examines the evidence supporting the use of metformin in other conditions such as PCOS, gestational diabetes, and metabolic syndrome. It may summarize findings from clinical trials and systematic reviews regarding its efficacy and safety in these populations.

Recent advancements in metformin research are highlighted, including novel insights into its mechanisms of action, potential benefits beyond glycemic control (e.g., cardiovascular risk reduction, anti-inflammatory effects), and emerging clinical applications in areas such as cancer prevention and treatment.The review addresses potential side effects and risks associated with metformin use, including rare but serious adverse events such as lactic acidosis. It may discuss risk factors for adverse effects and strategies for mitigating them, as well as controversies or areas of uncertainty regarding its safety profile.Finally, the review discusses future directions for research and clinical practice related to metformin. This may include ongoing clinical trials investigating its use in novel indications or combination therapies, as well as areas where further research is needed to optimize its efficacy, safety, and patient outcomes.

13. Conclusion

Metformin is the sole biguanide available in the United States and is a powerful agent that enhances insulin sensitivity. Its primary action is on hepatic glucose production, but it also has secondary effects on peripheral insulin sensitivity. The main antihyperglycemic effects of metformin are achieved by reducing hepatic gluconeogenesis, possibly by influencing mitochondrial calcium handling. Metformin has a remarkable safety profile and is effective as a standalone treatment or in combination with sulfonylureas, insulin, and thiazolidinediones. Unlike insulin, sulfonylureas, and thiazolidinediones, metformin does not lead to weight gain and may even cause weight reduction in obese patients. It appears to have significant positive effects on lipid metabolism, clotting factors, and platelet function. In animal studies, metformin has been shown to correct diabetes-induced cardiac diastolic dysfunction. Additionally, metformin improves vascular relaxation and likely decreases blood pressure in specific patients. These effects may contribute to improved cardiovascular mortality rates when used as monotherapy. The observations from the UKPDS study, which reported increased mortality during combination therapy with metformin and sulfonylureas, are likely due to the natural progression of type 2 diabetes rather than the therapy itself, and further clarification is needed.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflicts of interest.

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