Metformin: A Versatile Therapeutic Agent in Various Diseases and Health Conditions

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Metformin, a widely used medication for type 2 diabetes, has therapeutic effects beyond glycemic control. This literature review provides a comprehensive summary of metformin's mechanisms, clinical applications, and research progress in various health conditions, including its potential role in the management of COVID-19. The review covers the historical development of metformin and its efficacy in treating diabetes. It explores its mechanisms of action, including blood glucose reduction and improved insulin resistance. Furthermore, the review discusses metformin's applications in obesity, metabolic disorders, cancer, and cardiovascular disease. It highlights its potential to facilitate weight loss, decrease liver glucose output, enhance muscle glucose uptake, and contribute to cancer prevention and treatment. Additionally, metformin's protective effects against cardiovascular disease are addressed. Moreover, the review explores emerging research on metformin's anti-aging, anti-inflammatory, and antioxidant properties, expanding its therapeutic potential. This comprehensive review emphasizes metformin's significant therapeutic potential in various health conditions, including its potential role in the management of COVID-19. It calls for further investigation to better understand its mechanisms of action and optimize its clinical applications.

Keywords: metformin; therapeutic effects; covid-19; type 2 diabetes; long covid;

I. Introduction

Metformin is a widely used oral hypoglycemic agent that belongs to the biguanide class of drugs. It was first introduced in the 1950s as a treatment for type 2 diabetes mellitus, and it remains one of the most commonly prescribed medications for this condition today[1]. The use of metformin has been shown to significantly improve glycemic control, decrease insulin resistance, and reduce the risk of diabetes-related complications such as cardiovascular disease, neuropathy, and retinopathy[2].

Aside from its role in the management of diabetes, metformin has been studied extensively for its potential therapeutic effects in other areas of medicine. Research has suggested that metformin may have beneficial effects on weight loss, polycystic ovary syndrome, cancer, and cardiovascular disease[3]. Given the wide range of potential applications for metformin, it is important to review the available literature and understand the current state of knowledge on this drug.

II. Role of Metformin in the Treatment of Diabetes

Metformin is a first-line medication for the treatment of type 2 diabetes mellitus, and its mechanism of action is multifaceted[2]. Here we review the major mechanisms by which metformin lowers blood glucose and improves insulin resistance, as well as its potential impact on the development of diabetes.

Glucose-lowering mechanisms

Currently, it has been reported that metformin reduces hepatic glucose production and enhances glucose uptake in peripheral tissues by inhibiting the first complex of the mitochondrial respiratory chain, leading to an increase in AMP-activated protein kinase (AMPK) activity[4, 5]. However, the specific mechanism underlying AMPK activation by metformin remains elusive. Previous studies have shown that AMPK activation is mediated by liver kinase B1 (LKB1), a tumor suppressor, and calmodulin-dependent protein kinase kinase-β (CaMKKβ)[6, 7]. Moreover, in addition to the AMPK pathway, metformin has been reported to activate other signaling pathways such as the extracellular signal-regulated kinase (ERK) pathway and the phosphatidylinositol 3-kinase (PI3K) pathway, which are also involved in the regulation of glucose metabolism[8, 9]. Additionally, metformin increases intestinal glucose uptake and reduces glucose absorption in the gastrointestinal tract[10]. Metformin has been found to target AMP-activated protein kinase (AMPK) as a major mechanism of action for its clinical doses[11]. AMPK is a member of the transferases family that belongs to the class of serine/threonine kinases, which can be activated following a dip in intracellular ATP levels. AMPK exhibits numerous biological, metabolic, and physiological functions, and its activity leads to favorable physiological effects[12]. Upon activation of AMPK, metabolic adaption is facilitated by inhib-

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Table I *Potential applications of metformin in various health conditions*

Health Conditions	Potential Applications of Metformin	Description
Type 2 Diabetes	Regulate glucose metabolism and improve insulin sensitivity	First-line treatment option for improving glucose metabolism and insulin sensitivity.
Cancer	Inhibit tumor growth and reduce cancer incidence	Potential anticancer effects by inhibiting tumor growth and metastasis.
Cardiovascular Disease	Improve lipid metabolism and reduce the risk of cardiovascular events	Potential benefits in reducing the risk of cardiovascular events and improving lipid metabolism.
Aging-related Disorders	Activate AMPK, reduce inflammation and oxidative stress, and delay aging process	Potential anti-aging effects by reducing inflammation and oxidative stress.
Polycystic Ovary Syndrome	Regulate menstrual cycles and improve fertility	Investigated for its potential applications in various other health issues, such as polycystic ovary syndrome.
Nonalcoholic Fatty Liver Disease	Improve liver function and reduce hepatic steatosis	Investigated for its potential applications in various other health issues, such as nonalcoholic fatty liver disease.
Alzheimer's Disease	Reduce chronic inflammation and improve cognitive function	Potential applications in reducing chronic inflammation in conditions such as Alzheimer's disease.
Autoimmune Disorders	Reduce chronic inflammation and improve immune function	Potential applications in reducing chronic inflammation in conditions such as autoimmune disorders.
COVID-19	Improve outcomes in COVID-19 patients and reduce mortality rates	Investigated for its potential applications in various other health issues, such as COVID-19.

Table II *Summary of mechanisms by which metformin exerts its beneficial effects in different health conditions*

Health Condition	Mechanisms of Action
Type 2 diabetes	Decreased hepatic glucose production, increased peripheral glucose uptake, enhanced insulin sensitivity, improved beta-cell function
Cancer	Activation of AMPK pathway, inhibition of mTOR pathway, suppression of cancer cell growth and proliferation
Cardiovascular disease	Improvement of endothelial function, reduction of inflammation, inhibition of platelet aggregation
Aging-related disorders	Activation of AMPK pathway, inhibition of mTOR pathway, reduction of inflammation, improvement of mitochondrial function

iting anabolic ATP-consuming pathways such as protein synthesis and fatty acid synthesis and by promoting different catabolic ATP-generating pathways such as glycolysis, glucose uptake, and fatty acid oxidation. Moreover, AMPK induces inhibitory phosphorylation of TBC1D1, a Rab-GTPase activator, eventually enhancing the activity of Rab-family G proteins and fusion activity. AMPK also increases the mRNA expression of GLUT4- and hexokinase 2-encoded genes. It regulates the glycolysis and glycogenesis processes and inhibits CREB-regulated transcription coactivator 2 (CRTC2) and hepatocyte nuclear factor 4 (HNF4), which in consequence, inhibit gluconeogenesis. AMPK activation has also been found to exhibit insulin-sensitizing effects along with other health-promoting effects. Interestingly, metformin has been shown to inhibit the lysosomal proton pump v-ATPase, which is a central node for AMPK activation following glucose starvation. Metformin-bound PEN2 forms a complex with ATP6AP1, a subunit of the v-ATPase, which leads to the inhibition of v-ATPase and the activation of AMPK without effects on cellular AMP levels. Knockout of PEN2 in mice or re-introduction of a PEN2 mutant that does not bind ATP6AP1 blunts AMPK activation[11]. Thus, metformin's activation of AMPK through inhibition of v-ATPase is an important mechanism for its clinical effects.

Improvement of insulin resistance

Metformin has been shown to improve insulin sensitivity in peripheral tissues, such as skeletal muscle, by enhancing glucose uptake and utilization[13, 14]. This effect is thought to be mediated by increased AMPK activity and subsequent activation of the insulin receptor substrate (IRS) and Akt signaling pathways[15]. In addition to these pathways, other key molecules involved in insulin

Table III *Comparison of the effects of metformin with other antidiabetic medications on glycemic control, weight, and cardiovascular outcomes*

Medication	Glycemic Control	Weight	Cardiovascular Outcomes
Metformin	Effective	Neutral	Improved
Sulfonylureas	Effective	Increased	Neutral
DPP-4 Inhibitors	Effective	Neutral	Neutral
GLP-1 Receptor Agonists	Effective	Decreased	Improved
SGLT2 Inhibitors	Effective	Decreased	Improved

signaling may also be impacted by metformin treatment. For example, It also activates protein kinase C (PKC) isoforms, which play a role in the regulation of insulin signaling[16]. Furthermore, metformin treatment has been reported to increase the expression of IRS-1 and IRS-2, which are involved in the activation of downstream signalling pathways[17].

Metformin also enhances the uptake of fatty acids in the liver, which leads to a reduction in circulating free fatty acids and decreased insulin resistance[18, 19]. This effect is thought to be mediated by AMPK activation, which subsequently inhibits lipid synthesis and stimulates fatty acid oxidation[20]. Therefore, metformin's ability to regulate fatty acid metabolism may also contribute to its beneficial effects on insulin sensitivity.

Impact on the development of diabetes

Studies have suggested that early initiation of metformin therapy in individuals with impaired glucose tolerance can significantly reduce the risk of developing diabetes[21]. The United Kingdom Prospective Diabetes Study (UKPDS) showed that metformin treatment reduced the risk of diabetes-related endpoints by 32% compared to conventional therapy[22].

III. The role of metformin in the treatment of obesity

Metformin has been shown to have beneficial effects in the management of obesity. The following mechanisms have been proposed:

Mechanisms for weight reduction

Metformin reduces appetite and food intake by acting on the central nervous system, and promotes weight loss by increasing energy expenditure through activation of AMP-activated protein kinase (AMPK) in skeletal muscle and the liver[23].

Mechanisms for decreasing hepatic glucose output

Metformin reduces hepatic glucose output by inhibiting gluconeogenesis and glycogenolysis in the liver, which decreases the amount of glucose released into the bloodstream[23].

Mechanisms for increasing glucose uptake in muscle

Metformin increases glucose uptake in muscle by stimulating translocation of glucose transporters to the cell membrane and improving insulin sensitivity[23].

Overall, metformin has been shown to be effective in reducing body weight, improving insulin sensitivity, and decreasing the risk of type 2 diabetes in obese individuals[23]. However, further research is needed to fully elucidate the mechanisms underlying its effects on weight and metabolism.

IV. The application of metformin in the treatment of metabolic diseases

Mechanisms for the treatment of polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is fundamentally a hormonal disorder, but it gives rise to metabolic consequences. To address PCOS, metformin proves effective via several mechanisms. This medication diminishes insulin resistance and hyperinsulinemia—both prevalent in PCOS. Moreover, metformin ameliorates menstrual irregularities, fosters ovulation, and enhances fertility in affected women. This is achieved by mitigating androgen levels, a pivotal factor in PCOS symptoms[24].

Mechanisms for lowering high cholesterol and triglycerides

Metformin has been shown to reduce high levels of cholesterol and triglycerides in the blood. This is likely due to its ability to reduce hepatic gluconeogenesis and lower circulating insulin levels, which can lead to decreased synthesis of cholesterol and triglycerides in the liver[25].

Overall, metformin has shown promise as a treatment for metabolic diseases such as PCOS, as well as for improving lipid profiles in individuals with hyperlipidemia. However, further studies are needed to fully elucidate the mechanisms underlying these effects.

V. Metformin's Applications in Cancer Treatment

Metformin has been shown to have potential applications in cancer treatment through various mechanisms.

Prevention and Treatment of Breast Cancer:

Metformin has been found to reduce the incidence and mortality of breast cancer by decreasing insulin levels, inhibiting the mTOR pathway, and regulating the AMPK pathway[26]. Additionally, metformin can also increase the efficacy of tamoxifen, a commonly used breast cancer drug[27].

Prevention and Treatment of Colorectal Cancer:

Studies have shown that metformin can reduce the risk of colorectal cancer by up to 30%, and may also improve the prognosis of patients with colorectal cancer by inhibiting cancer cell proliferation and inducing apoptosis. This is likely due to the drug's ability to inhibit the Wnt signaling pathway and activate AMPK[28, 29].

Other Cancer Types:

Metformin has also shown potential in the treatment of other types of cancer, including pancreatic cancer, ovarian cancer, and prostate cancer. These effects are thought to be mediated by the drug's ability to regulate glucose metabolism, inhibit cancer cell proliferation, and induce apoptosis[26].

Several clinical trials are currently underway to investigate the efficacy of metformin in cancer treatment, including its potential to improve response rates to chemotherapy and reduce cancer recurrence rates.

VI. Metformin's Protective Effects on Cardiovascular Disease

Metformin has been found to have potential protective effects against cardiovascular disease through various mechanisms.

Metformin has been shown to reduce the risk of cardiovascular disease by improving insulin sensitivity, reducing inflammation, and lowering blood pressure. In addition, the drug can also improve lipid profiles by reducing low-density lipoprotein (LDL) cholesterol and increasing high-density lipoprotein (HDL) cholesterol levels[30].

Metformin has also been found to reduce mortality rates in patients with cardiovascular disease. This is likely due to the drug's ability to improve glucose control, reduce inflammation, and promote endothelial function[31].

Furthermore, metformin's potential therapeutic effects on other cardiovascular diseases, such as coronary artery disease and hypertension, can also be discussed with reference to relevant clinical research findings[32].

Several studies have found more evidence for the cardioprotective nature of metformin, including its potential to improve left ventricular mass index (LVMI) and systolic blood pressure (SBP), as compared to the placebo administered for the experiment. However, there is still a need for further investigation into the mechanisms underlying

Table IV *Comparison of potential side effects of metformin with other antidiabetic medications*

Side effects	Metformin	Sulfonylureas	DPP-4 inhibitors	GLP-1 receptor agonists	SGLT2 inhibitors
Hypoglycemia	Low risk	High risk	Low risk	Low risk	Low risk
Weight gain	Neutral to weight loss	Weight gain	Neutral to weight gain	Weight loss	Weight loss
Gastrointestinal issues	Common	Rare	Common	Common	Common
Cardiovascular outcomes	Potential benefit	Neutral	Neutral	Potential benefit	Potential benefit
Vitamin B12 deficiency	Possible	-	-	-	-
Lactic acidosis	Rare but serious	-	-	-	-

***Table V** Comparison of optimal doses and durations of metformin treatment for different health conditions*

Health Condition	Optimal Dose	Optimal Duration
Type 2 Diabetes[2]	1000-2000mg	Long-term
Polycystic Ovary Syndrome[39])	1500-2000mg	Long-term
Non-alcoholic Fatty Liver Disease[40])	1000-2000mg	6-12 months
Cardiovascular Disease Prevention[41])	850-1000mg	Long-term
Aging-related Disorders[42])	1000-2000mg	Long-term

Explanation of Acronyms:
Akt: Protein Kinase B; AMPK: Adenosine Monophosphate-Activated Protein Kinase; COVID-19: Coronavirus Disease 2019; GLUT4: Glucose Transporter 4; IRS: Insulin Receptor Substrate.

metformin's cardioprotective effects. One such mechanism involves the AMPK-FOXO-Trx pathway, which improves antioxidant defense and attenuates associated pathogenic processes like lipid peroxidation, impaired cardiomyocyte metabolism, and endothelial dysfunction, preventing a number of cardiovascular abnormalities. Another mechanism is the suppression of acetylcholinesterase (AChE) activity by metformin administration, which improves acetylcholine (Ach) levels and significantly inhibits morphological abnormalities of mitochondria, stimulating PGC-1α, a transcriptional coactivator, which regulates mitochondrial biogenesis and is directly linked with cardiac functioning. Furthermore, metformin has been found to keep the mitochondrial permeability transition pore closed via activating the AMPK pathway, preventing associated cell death in affected tissues under conditions of myocardial infarction (MI) and ensuing reperfusion. These leads to a reduction in the infarct size, resulting in better and faster recovery and survival rates of patients with cardiovascular disorders[12]. Overall, detailed information regarding the mechanisms underlying metformin's cardioprotective effects is necessary to fully understand its potential in suppressing cardiovascular events.

VII. Research Progress on Other Applications of Metformin

Metformin has shown potential applications in various areas beyond its traditional use in diabetes management.

Anti-aging, Anti-inflammatory, and Antioxidant Applications:

Recent studies have suggested that metformin may have anti-aging effects by activating AMPK and reducing inflammation and oxidative stress. In addition, metformin has also been shown to have potential applications in reducing chronic inflammation in conditions such as Alzheimer's disease and autoimmune disorders. According to Barzilai et al., "metformin is the first-line drug for the treatment of type 2 diabetes mellitus and has shown promise in increasing healthspan in humans"[33].

Other Health Issues:

Metformin has been investigated for its potential applications in various other health issues, such as polycystic ovary syndrome, nonalcoholic fatty liver disease, and even COVID-19. Although the mechanisms by which metformin may benefit these conditions are not fully understood, the drug's ability to regulate metabolism and reduce inflammation may play a role. Bramante et al. suggested that "metformin has been shown to reduce inflammation and improve immune function, making it a promising candidate for adjuvant therapy for COVID-19"[34].

Several recent studies have investigated the potential of metformin in the treatment of Covid-19. Ventura-López et al. (2022)[35] conducted an in vitro and clinical trial study to evaluate the effect of metformin glycinate (MG) on the viral load of SARS-CoV-2. The in vitro results demonstrated a significant reduction in viral load with MG treatment. In the clinical trial, Covid-19 patients treated with 620 mg of MG every 12 hours showed a safe and significant decrease in viral load. These findings suggest that MG could be a potential treatment option for SARS-CoV-2. However, further clinical studies are needed to establish the safety and efficacy of MG in larger populations, considering the limitations of the study, such as the hospitalization condition of the patients and the need for longer follow-up to assess its impact on subacute and chronic complications of COVID-19 patients. In another study, Bramante et al. (2022) [36] investigated the outpatient treatment of Covid-19 using a combination of metformin, ivermectin, and fluvoxamine. The results showed that metformin significantly reduced the development of Long Covid by 42% in vaccinated individuals, even during the Omicron wave. This finding is significant, considering the potential long-term health, mental health, and economic consequences of Long Covid, particularly among socioeconomically marginalized groups. Additionally, the trial demonstrated a reduction in emergency department visits, hospitalizations, or death with metformin treatment, further supporting its potential as a therapeutic option. However, additional clinical trials are necessary to explore potential synergies with other treatments and evaluate its efficacy in different populations. These studies highlight the potential of metformin in reducing viral load, preventing Long Covid, and improving clinical outcomes in Covid-19 patients. However, further research is warranted to validate these findings, assess the optimal dosage and treatment duration, and explore its potential in combination with other therapeutic interventions.

While further research is necessary to fully explore these potential applications, the wide range of health benefits associated with metformin make it a promising candidate for future research and development.

VIII. Conclusion

Metformin has been extensively researched for its therapeutic effects in the management of type 2 diabetes. The drug's ability to regulate glucose metabolism and improve insulin sensitivity has made it a first-line treatment option for patients with this condition[3]. However, recent studies have also suggested that metformin may have potential applications in various other health issues, such as cardiovascular disease, cancer, and aging-related disorders[37, 38].

Despite the promising results, there are still challenges and limitations that need to be addressed in the future research of metformin. One of the challenges is to identify the optimal dose and duration of treatment for different conditions, as well as to investigate the potential side effects associated with long-term use. Furthermore, the mechanisms by which metformin exerts its beneficial effects in these conditions are not fully understood, and more research is needed to elucidate the underlying pathways.

In summary, metformin is a widely used and well-studied drug with a broad range of potential applications beyond its traditional use in diabetes management. Further research is necessary to fully explore its therapeutic potential, address the challenges and limitations, and optimize its use in different clinical settings.

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