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Pharmacological Mechanisms and Emerging Therapeutic Applications of Metformin

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Abstract. Metformin is one of the most widely used medications for the treatment of type 2 diabetes mellitus. Its principal glucose-lowering properties are related to the inhibition of hepatic gluconeogenesis and enhancement of peripheral insulin sensitivity. At the same time, growing data indicate that metformin might affect the intestines, gut microflora, cell metabolism, inflammation, oxidative stress, and autophagy. The present review aims to discuss the pharmacodynamics and pharmacokinetics of metformin, its clinical applications, adverse effects, and future perspectives. Special focus is made on the possible cardiovascular protective, anti-inflammatory, anticancer, anti-ageing, and polycystic ovary syndrome properties of metformin. The current evidence base allows asserting that metformin is well-established for type 2 diabetes mellitus, preventive treatment of prediabetes in selected populations, and management of certain metabolic disorders in Polycystic Ovary Syndrome (PCOS). Nevertheless, there is not enough evidence for using metformin as a means of cancer and cardiovascular disease prevention, as well as healthy ageing. Patient-specific factors, dosing, and exposure can be considered as possible causes for different results of treatment. In general, metformin is still one of the key medicines for metabolic disorder treatment, while well-conducted randomized clinical trials are required to validate its new indications and promote personalized treatment approaches.

Keywords: metformin, type 2 diabetes mellitus, drug repurposing, AMPK

1. Introduction

Type 2 diabetes mellitus (T2DM) continues to be a serious global health problem, which is defined by the development of insulin resistance and metabolic disturbances [1]. Metformin belongs to the most effective hypoglycemics, and its role as a first-line pharmacological therapy for T2DM treatment is recognized worldwide [2]. Its extensive use in clinical practice is due to its powerful glucose-lowering properties, minimal risk of hypoglycemia in case of monotherapy, neutral weight profile, and low price.

The classic mechanism of metformin therapy lies in its ability to reduce the formation of glucose in the liver because of inhibition of gluconeogenesis [1, 3] and increased peripheral insulin sensitivity in skeletal muscle and adipose tissues [4]. Recently, additional mechanisms were identified, such as the activation of Glucagon-Like Peptide-1 (GLP-1) release and modulation of the gut microbiota and AMP-activated protein kinase (AMPK) pathways in the lysosomes [5]. Besides

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glucose metabolism, growing basic and clinical data point out a wide range of non-glycemic beneficial pharmacological effects of metformin [1]. These include cardioprotective effects [6], anti-inflammatory and antioxidant effects [7], therapy of polycystic ovary syndrome (PCOS) [8], and some oncolytic and gerontological possibilities [9, 10].

However, despite these encouraging prospects for therapy, there are still substantial translational challenges [11]. Molecular pathways established in laboratories often depend on doses that are higher than those seen clinically [12]. Furthermore, the presence of marked inter-patient variations in clinical efficacy and tolerance makes the pharmacokinetics and pharmacogenetics of the drug rather complex. In order to account for these issues, this paper gives a detailed analysis of metformin's pharmacology and clinical dosing guidelines [2]. In particular, the paper focuses on discussing the drug's broadened therapeutic possibilities for non-diabetes disorders and existing problems in translational research [11]. Future research perspectives towards personalized medicine and clinical trials are also mentioned.

2. Pharmacological mechanisms of metformin

2.1. Hepatic mechanism

The main antihyperglycemic effect of metformin is associated with decreased production of glucose via suppression of hepatic gluconeogenesis, which is the process of the synthesis of glucose from some precursors by the liver. People with type 2 diabetes produce excess glucose because of insulin resistance of the liver [1]. Most of the antidiabetic effect of metformin is due to its ability to reduce hepatic glucose production by 20%—30% [3]. The mechanism of action of metformin is the suppression of the mitochondrial glycerol-3-phosphate dehydrogenase (GPD2), which leads to the increased ratio of cytosolic Nicotinamide Adenine Dinucleotide (NADH)/Reduced Nicotinamide Adenine Dinucleotide (NAD+), which leads to the decreased gluconeogenesis from glycerol and other redox-dependent substrates. Metformin also raises the concentration of adenosine monophosphate (AMP), which inhibit fructose-1,6-bisphosphatase (FBP1), which inhibits gluconeogenesis. This is the substrate-selective inhibition of gluconeogenesis hypothesis to explain why metformin does not cause hypoglycemia in monotherapy [13].

2.2. Peripheral mechanism

Metformin increases the sensitivity of the peripheral tissues (skeletal muscle and adipose tissue) to insulin, thus improving the sensitivity of insulin to its target tissues and promoting increased uptake and utilization of glucose. Metformin is a molecule that works on the molecular level by inhibiting the negative regulator of insulin signaling, SH2 domain-containing inositol polyphosphate 5-phosphatase 2 (SHIP2). The inhibition of SHIP2 leads to activation of phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathway, which increases glucose transporter type 4 (GLUT4) translocation to the cell membrane and glucose uptake [4]. Insulin sensitivity has an important clinical value, since insulin resistance is a key pathophysiological characteristic of type 2 diabetes. Metformin does not directly stimulate insulin production, but instead improves the sensitivity to insulin. Metformin improves insulin sensitivity, and this is an important pathophysiological mechanism of type 2 diabetes. This is also why metformin does not directly affect insulin secretion and is considered to have a low risk for hypoglycemia [2].

DOI: 10.54254/2753-8818/2027.MB38919

2.3. Intestinal mechanism

It has been established that the gastrointestinal system is an emerging site in which metformin exerts its effects. Metformin was found to increase the level of GLP-1, which may be one of the ways that it induced glucose-lowering effects [1]. Metformin can lead to a rise in growth differentiation factor 15 (GDF15) levels in circulation, which is believed to cause appetite suppression and weight loss. Moreover, metformin leads to significant modifications of the gut microbiome, namely increases the levels of beneficialial bacteria, including Akkermansia muciniphila and bacteria producing short-chain fatty acids [4]. All of these changes may result in improved metabolic health by optimizing intestinal barrier integrity, lowering systemic inflammation, and changing bile acids metabolism. Whether the changes in gut microbiome associated with metformin treatment are responsible for the gastrointestinal symptoms such as diarrhoea and bloating is unknown.

2.4. AMPK pathway

AMP-activated protein kinase (AMPK) is a sensor and regulator of cellular energy. Much of the activity of metformin is AMPK independent, but the activation of AMPK is a key activity involved in the metabolism. In the traditional model, metformin was thought to inhibit the mitochondrial complex I, resulting in the elevation of the ratio of AMP/ adenosine triphosphate (ATP) and subsequent activation of AMPK. Most of the evidence for direct complex I inhibition was provided with supratherapeutic concentrations that are not reached in vivo [12]. A pioneering study showed that therapeutic concentrations of metformin can bind to PEN2 and stimulate the association of PEN2 with the v-ATPase complex and AMPK activation via the lysosomal pathway [5]. Moreover, metformin also works in AMPK-independent ways, namely, the rise in the AMP concentration could lead to decreasing the level of cyclic adenosine monophosphate (cAMP) and inhibit the activity of adenylate cyclase and thus suppress the action of glucagon on glucose production [4].

3. Current clinical application and prescribing standard

3.1. First-line monotherapy for type 2 diabetes

Currently, metformin is considered a highly recommended first-line pharmacotherapy for type 2 diabetes, but more contemporary recommendations put emphasis on personalized treatment depending on the presence of other comorbidities and specific patient features. The advantages of metformin include efficient decrease in glycated hemoglobin A1c (HbA1c) levels, lack of hypoglycemia risks with monotherapy, absence of significant weight gain risks, low cost, and great experience in using metformin long-term [2]. Metformin is usually prescribed with initial low doses, which can then be adjusted according to tolerability and kidney functionality, and common doses range from 1,500 to 2,000 mg/day [14]. Additionally, there are extended-release formulas of metformin which improve tolerability in the gastrointestinal (GI) tract and make once-a-day administration of the drug possible in some patients [14]. The results of a systematic review conducted in the Asian population confirmed the efficacy of the drug [2]. Thus, the results of the literature review prove that metformin still plays a significant role in the management of T2DM, especially where cost-effectiveness and clinical experience play a crucial role.

DOI: 10.54254/2753-8818/2027.MB38919

3.2. Combination therapy

The development of T2DM is a progressive disease, and the majority of patients require combination therapy depending on the effects of this drug on cardiovascular, kidney, weight, and other comorbidities in order to achieve good glycemic control. Metformin is the basis for almost all combination strategies, and the drug can be successfully combined with other glucose-lowering drugs, including sulfonylureas, (dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose contransporter 2 (SGLT2) inhibitors, GLP-1 receptor agonists, and insulin in order to manage glycemic levels in adults with T2DM in the Asian population. Clinical decisions regarding additional therapy must take into account glycemic control, clinical, and treatment characteristics of a patient. In the Asian population, metformin-based combination therapy is widely used, and the combination of metformin and sulfonylureas is regarded as one of the most popular combinations. The results of the review prove the effectiveness of metformin-based combination therapy in achieving and maintaining glycemic control. Thus, if monotherapy with metformin is not enough, adding a second glucose-lowering agent will provide an effective way to achieve treatment targets while adjusting therapy to the individual characteristics of a patient [2].

3.3. Preventive intervention in Prediabetes

Prediabetes is diagnosed in the case of impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and/or the increased HbA1c level of 5.7–6.4% in patients that have an increased risk of developing type 2 diabetes [15]. Nevertheless, the recommended preventive strategy remains a healthy lifestyle; however, metformin can be considered as an additional preventive therapy in patients with a high risk of progressing to the disease. The results of the Diabetes Prevention Program (DPP) revealed that the risk of the development of type 2 diabetes decreased by about 31% over three years when taking metformin in comparison with placebo. Metformin therapy proved to be especially effective in younger patients and with body mass index (BMI) ≥35 kg/m², as well as in people with a history of gestational diabetes [15]. Based on that, the current recommendation by the American Diabetes Association (ADA) suggests using metformin in adults who have high risks of type 2 diabetes mellitus, particularly those who are aged from 25 to 59 years with BMI ≥35 kg/m², high fasting glucose, and HbA1c ≥6.0%, as well as those with a history of gestational diabetes [15]. Liu et al. used to discuss the potential effectiveness of metformin in prediabetes but emphasize the lack of information about its dosing, side effects, and evidence base. Thus, metformin can be used in selected high-risk patients with prediabetes but not universally [16].

3.4. Adverse effects

Metformin is generally well tolerated, but it has several notable adverse effects and contraindications that clinicians must consider. Gastrointestinal side effects are the most common, affecting approximately 20–30% of patients, with symptoms including diarrhoea, nausea, vomiting, and abdominal discomfort. These effects are dose-dependent and usually occur when treatment is initiated. They can be minimised by starting with a low dose (500 mg daily), taking the drug with meals, and using extended-release formulations, which are now cheaper and preferred according to National Institute For Health and Care Excellence (NICE).

Lactic acidosis is a rare but serious adverse effect, with an estimated incidence of 1 to 5 cases per 100,000 patient-years. It occurs when metformin accumulates to toxic levels, typically in patients with severe renal impairment (estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m²),

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advanced liver disease, or conditions causing tissue hypoperfusion, such as heart failure or sepsis [17]. Metformin is contraindicated in these patients. For patients with eGFR 30–44 mL/min/1.73m², the dose should be reduced to a maximum of 1,000 mg daily.

Vitamin B12 deficiency is another concern with long-term use. Metformin interferes with vitamin B12 absorption in the terminal ileum, and long-term therapy may lead to megaloblastic anaemia and peripheral neuropathy. The American Diabetes Association recommends periodic monitoring of B12 levels in patients on long-term metformin therapy [15]. In summary, while metformin is safe for most patients, careful attention to renal function, dose titration, and long-term monitoring is essential.

4. Expanded pharmacological effects

4.1. Cardiovascular protective effects

It is reported that cardiovascular disease is one of the main causes of illness and mortality among diabetic patients [6]. Hyperglycemia, insulin resistance, dyslipidemia, endothelial dysfunction, and chronic low-grade inflammation may interact together and ultimately promote atherosclerosis and cardiovascular diseases [18]. Therefore, research into the cardiovascular safety and cardioprotective activity of glucose-lowering agents is essential.

For a long time, the cardiovascular protection by metformin was regarded as a result of metformin's indirect effects, such as reduction of hyperglycemia, improvement of insulin resistance, and weight control. However, emerging evidence suggests that metformin may possess cardioprotective effects which are partially unrelated to its ability to lower blood glucose [1].

Mechanistically, metformin may provide cardiovascular benefits through multiple mechanisms. Firstly, it improves insulin resistance, reduces glucose production, and exerts beneficial effects on body weight and lipid metabolism [1]. The improvement of blood glucose, insulin, and lipid metabolism may alleviate the metabolic stresses put on blood vessels in the long run [18].

Metformin inhibits the function of mitochondrial complex I and regulates cellular energy state, resulting in the change of the AMP/ATP ratio and activation of AMPK-related pathways [12]. AMPK-related pathways regulate the energy metabolism of cardiac and endothelial cells, reduce mitochondrial dysfunction and oxidative stress, and thus may play a role in protection of endothelial function and inhibition of atherosclerosis. Meanwhile, the effects of metformin on abnormal blood lipids, chronic low-grade inflammation, and visceral fat mass may contribute to its potential cardiovascular protection as well [18]. The cell and animal studies demonstrated that metformin may reduce ischemia-reperfusion injury, inhibit cardiac fibrosis, and improve cardiac function.

The umbrella review conducted by Bahardoust et al., which involved several systematic reviews and meta-analyses, showed that metformin therapy resulted in a decrease in the risk of all-cause mortality, cardiovascular mortality, and development of new cardiovascular events in comparison with placebo or sulfonylureas, as summarized in Table 1 [6]. The pooled effect estimates (odds ratio (OR)) for all-cause mortality, cardiovascular disease (CVD) mortality, and incident total CVD are presented in Table 1, with OR values for all-cause mortality and cardiovascular mortality reported as 0.800 and 0.771, respectively. To sum up, the value of OR less than 1 indicates that the probability of occurrence is lower in the metformin group in comparison with the control group. Thus, the above-mentioned findings prove the presence of cardiovascular protection by metformin. Metformin can have positive effects on patients with atherosclerotic cardiovascular disease and heart failure. Nevertheless, most previous studies were small and conducted at the time when SGLT2 inhibitorsors

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and GLP-1 receptor agonists were not widely used. Thus, the effect should be investigated in the context of the current treatment [18].

Table 1. Summary of the meta analysis results by pooling all the datasets in patients with and without metformin (placebo/control/sulfonylurea) [6]

Type	Number of studies	Number of total participants	Effect estimate (OR)	95% CI Cl-	P-value	I_2 value (p)
All-cause mortality	168	171,224	0.80	0.744-0.855	0.001	66.5% (0.001)
CVD mortality	123	2,214,132	0.771	0.690-0.894	0.001	67.4% (0.001)
Incident total CVD	105	1,526,211	0.828	0.781-0.875	0.001	15.8% (0.3)

4.2. Metabolic - syndrome - related regulatory effects

Metabolic syndrome is a clinical condition characterized primarily by central obesity, elevated blood glucose levels, altered blood lipid profile, and high blood pressure. Metabolic syndrome is a serious risk condition for the development of type 2 diabetes and atherosclerotic cardiovascular disease [2]. As metabolic disorders are interrelated in many ways, the metabolic syndrome is frequently accompanied by an increased risk of diabetes, fatty liver, and cardiovascular disease [1].

Insulin resistance is one of the major problems. This implies that while the body produces enough insulin, the body's tissues—muscle, fat, liver cells—cannot respond properly to insulin. Thus, metabolism of glucose and lipids becomes impaired gradually [1]. The most valuable effect of metformin in metabolic syndrome is that the drug affects insulin resistance, which is a significant factor in the development of metabolic syndrome. Metformin can inhibit hepatic gluconeogenesis and thus reduce glucose production by the liver and release of glucose into the blood. Also, the drug can increase insulin sensitivity of peripheral tissues and thus increase utilization of glucose in the muscles. Improved glucose and insulin levels lead to decreased stress on adipose tissue and liver from hyperinsulinemia.

Apart from reducing blood glucose, metformin is also associated with some positive effects on weight, visceral fat, and lipid profile of patients [12]. AMPK plays a role in fat synthesis and fatty acid oxidation. Therefore, through its action in this pathway, metformin may reduce synthesis of fat in the liver, increase use of fatty acids for energy, and reduce excess fat accumulation in the liver and visceral tissues. However, metformin's effects on weight and lipid levels are modest, and it should not be regarded as an equivalent of specific weight loss or lipid-lowering medications [1].

For individuals with prediabetes or with an increased risk of diabetes development, metformin can also slow down the deterioration of glucose metabolism [2]. Through improvement of insulin sensitivity and reduction of blood glucose levels, metformin can reduce the risk of long-term adverse effects of hyperglycemia on blood vessels, kidneys, and the nervous system. Thus, metformin can be viewed as the fundamental metabolic therapy in the management of metabolic syndrome, especially in individuals with obesity, glucose intolerance, or significant insulin resistance.

DOI: 10.54254/2753-8818/2027.MB38919

4.3. Anti-inflammatory and antioxidant effects

Inflammation and oxidative stress are typical pathophysiological phenomena in many chronic diseases [7]. In simple terms, oxidative stress may be considered as a state in which there are too many reactive oxygen species produced by cells, and these substances cannot be eliminated in an effective manner. They may ultimately result in cell membrane, protein, and DNA damage. Long-lasting elevated blood glucose levels, fat accumulation, and abnormal mitochondrial function can contribute to increased oxidative stress. On the other hand, oxidative stress can further enhance the inflammatory response. Thus, oxidative stress and inflammation may reinforce each other and be involved in chronic injuries of blood vessels, kidneys, the liver, and the nervous system.

Metformin is likely to reduce oxidative stress and inflammation through improvement of energy metabolism [1]. Firstly, this medicine can influence mitochondrial function and can inhibit excessive formation of reactive oxygen species when metabolic abnormalities are present. Secondly, metformin is also capable of modulating inflammatory signalling and autophagy via AMPK pathways [7]. Autophagy is a process during which cells degrade and recycle their components that were damaged. Normal autophagy ensures the proper functioning of the cells [12]. Regulation of such processes by metformin can explain its potential protective properties.

In the liver, metformin may contribute to improvement of insulin resistance and reduction of fat accumulation and inflammation [1]. In the case of kidneys, there are studies on cells and animals that suggest that metformin may decrease kidney damage and fibrosis associated with diabetes [12]. Regarding blood vessels and the heart, metformin may contribute to better endothelial function, reduce oxidative damage, and decrease the effect of inflammation on the cardiovascular system. With respect to the nervous system, there is ongoing research in the area of metformin's influence on neuroinflammation and mitochondrial dysfunction.

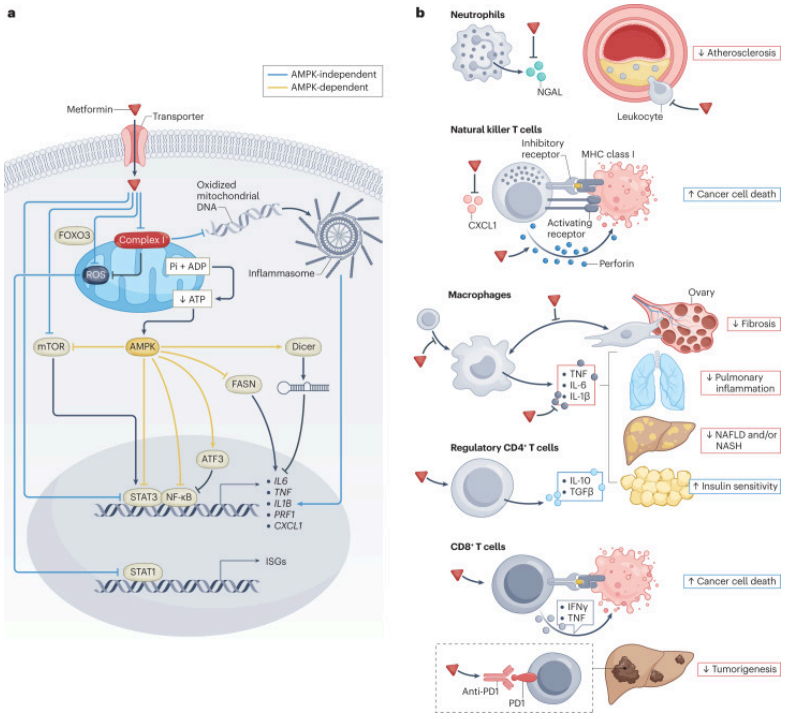


Figure 1. Cellular molecular mechanisms and tissue-specific immunomodulatory actions of metformin [19]

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(a) AMPK-Dependent and AMPK-Independent regulation of inflammatory signaling and cellular stress responses by metformin
(b) Tissue-Specific immunomodulatory effects of metformin on immune cells and organ fibrosis

The cellular molecular mechanisms and tissue-specific immunomodulatory effects of metformin are illustrated in Figure 1. Specifically, as shown in Figure 1a, metformin acts through both AMPK-dependent and AMPK-independent pathways to modulate transcription factors such as nuclear factor kappa B (NF-κB), signal transducer and activator of transcription 3 (STAT3), and forkhead box O3 (FOXO3), thereby regulating inflammatory cytokines (e.g. tumor necrosis factor (TNF), interleukin-6 (IL-6), interleukin-1 beta (IL-1β)) and cellular stress responses. Furthermore, Figure 1b highlights the broad immunomodulatory impacts across diverse cell types—including neutrophils, NK cells, macrophages, and T cells—ultimately contributing to reduced atherosclerosis, tissue fibrosis, and inflammatory damage in various organs [19].

4.4. Additional treatment for polycystic ovary syndrome

Polycystic ovary syndrome is a relatively frequent endocrine and metabolic disease in fertile-age females [8]. The basic characteristics include menstrual disorders, ovulation difficulties, and/or excess androgens. Besides, the disorder is also linked to obesity, insulin resistance, abnormal glucose tolerance, and dyslipidemia. Polycystic ovary syndrome is not merely a reproductive problem; it is also linked to metabolic problems. In this case, the use of metformin is justified. Insulin resistance can cause increased levels of insulin in the body [8]. These increased levels of insulin may stimulate androgen production by the ovaries and decrease sex hormone-binding globulin production, which leads to an increase in free androgen concentration in the blood. The elevated androgen levels can interfere with follicle formation and ovulation, causing menstrual irregularities [8]. Thus, metformin can help in lowering the cycle of insulin resistance, increased androgen levels, and ovulation difficulties.

According to the 2023 International Evidence-based Guideline for PCOS, metformin can be used for adults with PCOS and a BMI of ≥25 kg/m² to improve weight-related, insulin resistance, glucose, and lipid outcomes [9]. For those patients whose BMI is below 25 kg/m², the use of metformin may also be taken into account on an individual basis. This fact proves that the major aim of metformin in PCOS is the improvement of metabolic conditions.

4.5. Progress in basic research on anti-cancer effects

One important difference between cancer cells and normal cells is that their metabolism is altered [1]. To grow and divide rapidly, tumour cells require large amounts of energy and nutrients. They therefore change the way they use glucose, produce fatty acids, and use mitochondria. Since metformin can affect cellular energy metabolism, researchers have become interested in whether it can limit tumour growth.

From a mechanistic point of view, metformin may have two main types of effects. The first is an indirect effect: it lowers blood glucose and insulin levels [12]. Insulin and insulin-like growth factors can promote the growth of some tumour cells. Therefore, in patients with obesity, insulin resistance, or high insulin levels, metformin may indirectly reduce signals that support tumour growth by improving the overall metabolic environment [12].

The second is a direct effect. Metformin may affect mitochondrial complex I, which can reduce the energy supply of tumour cells. As depicted in Figure 2, metformin activates AMPK via liver kinase B1 (LKB1), which subsequently inhibits mechanistic target of repamycin (mTOR) signaling by phosphorylating tuberous sclerosis complex 1/2 (TSC1/2) and Raptor [20]. This cross-talk

DOI: 10.54254/2753-8818/2027.MB38919

downregulates protein and lipid synthesis, inhibits hypoxia-inducible factor 1-alpha (HIF1α)-mediated aerobic glycolysis and angiogenesis, and suppresses tumor cell growth and invasion (Figure 2) [9, 20].

Some cell and animal studies have found that metformin may inhibit tumour cell growth, cause cell-cycle arrest or cell death, and affect inflammation and immune responses around tumours [9]. However, it is important to note that the concentrations of metformin used in laboratory experiments are sometimes higher than the concentrations normally reached in human treatment. Therefore, experimental findings cannot be directly considered evidence of clinical effectiveness.

In clinical research, some observational studies have found that diabetic patients taking metformin may have a lower risk of developing certain cancers or dying from cancer [21]. A systematic review and meta-analysis published in 2025 also found an association between metformin use and a lower risk of some cancers. However, the results were not consistent across different cancer types, and the certainty of the evidence varied. One possible reason is that patients taking metformin may already differ from those not taking it in terms of diabetes severity, body weight, lifestyle, access to healthcare, and use of other glucose-lowering drugs. These differences may affect the study results [9].

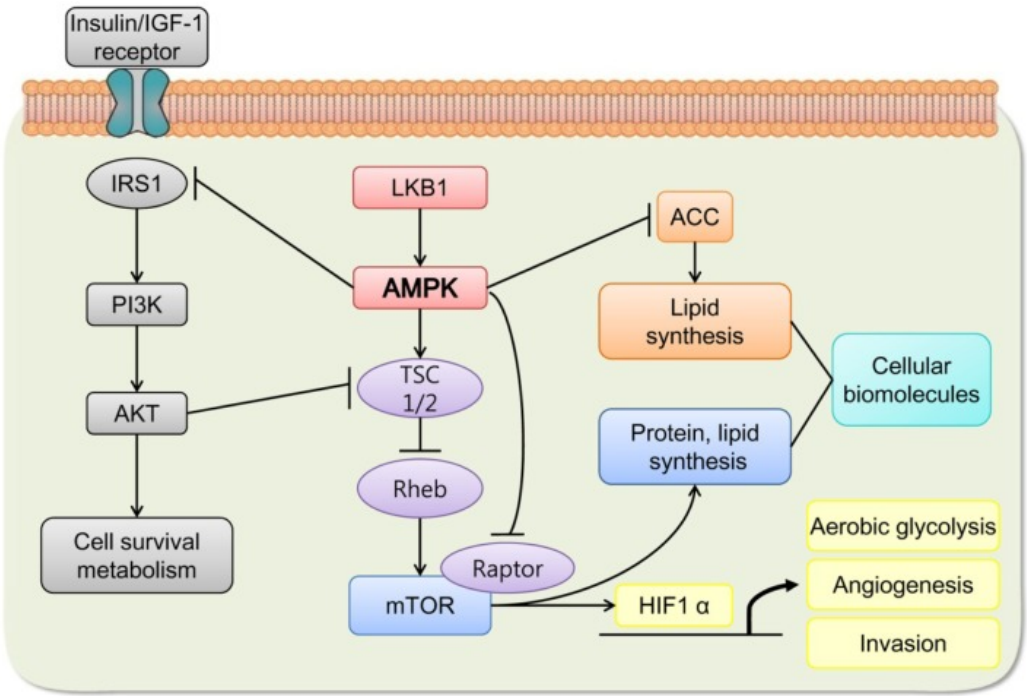


Figure 2. Interaction of AMPK with cancer metabolism [20]

4.6. Potential anti-ageing and cell-protecting effects

Ageing is due to multiple biological processes over the course of an orgaanism's life, including decreased function of mitochondria, chronic inflammation, oxidative stress, cell repair, and metabolic regulation [10]. Since metformin is able to influence energy metabolism, AMPK, and mTOR pathways that are associated with ageing, scientists decided to research if it can slow down the process of ageing or prevent age-related diseases.

Anti-ageing effects of metformin are mostly based on the theory of nutrient sensing [10]. Cells are able to regulate their growth, repair, and autophagy depending on the amount of energy and nutrients they have. AMPK is activated in cases of low energy in the cells and helps in preserving

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the balance and maintaining stability of the cells. mTOR is associated with cell growth and protein synthesis. By influencing these pathways, metformin could help cells remain in a stable condition. Metformin is also able to reduce oxidative stress, chronic inflammation, and mitochondrial dysfunction.

Animal and cell studies have shown that metformin can improve metabolism, reduce cellular damage, or extend lifespan in some experimental models [10]. However, an increase in lifespan in animals does not mean that the same effect will occur in humans. Human ageing is affected by many factors, including genetics, diet, physical activity, disease, and the social environment. Long-term follow-up is also needed to determine whether a drug can truly improve healthy lifespan. Current research0 mainly suggests that metformin may affect some ageing-related mechanisms or may be associated with a lower risk of certain age-related diseases in people with diabetes. However, there is not enough evidence to show that metformin can extend lifespan in healthy people.

5. Discussion

5.1. Mechanism behind the expanded effects of metformin

In fact, the glucose-lowering action of metformin may be mediated by the effect of metformin on reducing liver glucose production, on improving insulin resistance, and also on the metabolic effect on cells. However, metformin has other beneficial effects such as cardioprotection, anti-inflammatory effects, anticancer effects and anti-aging effects. It is suggested that these effects can be linked to the action of mitochondria, AMP-kinase, mTOR, microflora of the intestine, oxidative stress, autophagy, immune and inflammatory responses [11]. None of these pathways are standalone and may be interconnected in various diseases and tissues.

One of the most popular theories is that of metformin's effect on mitochondrial complex I and cellular energy state. In fact, the ratio of AMP/ATP might be altered in the presence of metformin, and then the AMPK pathway might be activated. AMPK is one of the key energy sensors that could impact the control of lipid metabolism, protein biosynthesis, autophagy, oxidative stress and inflammation [12].

However, the AMPK pathway is not the only way by which metformin works. The effect of metformin on hepatic glucose production and mitochondrial function and cell signalling may be independent of AMPK [22]. Moreover, the concentration of the drug as well as the process of drug uptake can differ between tissues. So, it is not possible that the same mechanism should cause all these effects in liver, heart, cancer and nervous tissues.

Another significant difference, and this is the one that I was concerned with the most, is that between lab experiments and treatment of a human. For some cell studies, the metformin concentrations are much higher than the level achieved in patients when they are treated normally. Therefore, the effects seen at high concentrations, particularly anti-cancer and anti-ageing effects cannot be attributed to human cases [11].

5.2. Challenge in clinical application

The long-term use of metformin includes its application in PCOS, cardiovascular diseases, cancer, age-related diseases, and neurological diseases. It has to be taken as read, however, that these conditions have their own disease mechanisms, treatment goals, patient characteristics, and conventional therapy. In this respect, it is not possible to apply the same treatment method which is applied in diabetes to these diseases [11].

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The key hurdle of research in this area is that these studies are conducted in a variety of patient groups, with varying doses of metformin, treatment durations, control groups, and endpoints. In cancer prevention studies, researchers can focus on the study of cancer incidence, tumour progression, and survival, whereas in anti-ageing studies they can focus on the study of inflammatory processes, metabolism, cognitive function, and ageing-related diseases [11]. It is hard to parallelize research and to arrive at a single conclusion.

Furthermore, the dose and the length of treatment vary for different uses. It has to be emphasized that metformin has a specific dose regime in type 2 diabetes, which may not be effective in other situations. In addition, increased doses can cause such problems as gastrointestinal symptoms, vitamin B12 deficiency, and lactic acidosis [1, 2]. Thus, the dose cannot be increased just to gain additional benefits.

As far as the new indications are concerned, PCOS appears to be more certain with regard to clinical guidelines. However, metformin was recommended in the 2023 International Evidence-based Guideline for PCOS to improve insulin sensitivity, glucose, lipid profile, and glucose and lipid metabolic effects in PCOS patients with a BMI of ≥ 25 kg/m^2 [6]. However, it is noteworthy to mention that not every woman suffering from PCOS requires taking metformin.

Concurrently, no established evidence exists for metformin use for the prevention of cardiovascular diseases, treatment of cancer, or anti-ageing. Although some observational studies suggested positive effects, they could not completely rule out the presence of confounding factors. Therefore, randomized controlled trials need to be performed prior to the acceptance of these indications in the clinic.

5.3. Individual differences and precision medicine

Patients do not all respond in the same way to the effects of metformin. Some have a clear drop in blood glucose levels, while others have a milder response. Likewise, some do not have any problem with the medication, but some experience side effects like nausea and diarrhoea [11]. These could also be relevant to the possible use of metformin in its new areas of application.

There could be several reasons for these variations, which include age, body mass, kidney health, diabetes duration, and pancreatic health. There could also be some genetic differences. Organic Cation Transporter 1 (OCT1), whose gene is Solute Carrier Family 22 Member 1 (SLC22A1), is a protein that helps metformin be taken up into liver cells [10]. There are studies that have found a link between the variant forms of SLC22A1 and decreased metformin uptake and lower glucose-lowering effect. Yet, the results differ in different populations, so OCT1 genetic testing is not recommended for now [9].

There may be interactions between metformin and the gut microbiota in relation to the patient's response to metformin. Metformin can affect the bacterial profile and the by-products produced by bacteria in the gut, while the gut microbiota can also be affected by diet, obesity, age, antibiotics, and the presence of disease [11]. However, further research in this area is required before this approach can be used clinically.

Accordingly, there is a need for future research to shift from an emphasis on "average treatment effect" to "patients most likely to respond." A combination of clinical factors, metabolic factors, gut microbiota, genetics, kidney function, and co-medications can potentially help to identify patients that are more likely to derive benefits or experience adverse effects. This would help to repurpose metformin into a more personalized form of therapy.

DOI: 10.54254/2753-8818/2027.MB38919

6. Conclusion

6.1. Deepening basic research

All of these mitochondrial, energy, AMPK-related, inflammatory, oxidative, and autophagic effects may be linked together and provide one of the main reasons why metformin may have multiple effects. But how it spreads is not yet well understood. Some studies are centered on the effect of metformin on mitochondrial complex I and the AMP/ATP ratio and then the activation of AMPK. In other studies, its actions have not been found to require AMPK activity, and it has been shown to vary as a function of both drug concentration and cell type, metabolic state, and disease model.

Future basic research needs to focus greater attention on the possibility of such mechanisms occurring in humans under actual conditions. Relatively high concentrations of metformin are used in some of the cell studies, and standard treatment may result in much lower concentrations in the blood and tissues of humans. Thus, the molecular effects seen in a laboratory experiment may not necessarily be directly translatable to a patient. Future research should involve an integration of pharmacokinetic information, tissue distribution, and cellular metabolism in different tissues to account for the actual exposure and its biological effects of various doses of metformin in tissues, including liver, intestine, muscle, cardiovascular, and tumour tissue.

Further studies will also need to shift their focus from single signalling pathways to a multi-pathway approach. For instance, the function of mitochondria, the AMPK/mTOR pathway, inflammatory markers, oxidative stress, gut microbiota, and metabolic changes can be studied in a combined approach. This might account for the different effects of metformin in different diseases. For research in anti-cancer and anti-ageing, it is crucial to understand if the effect of metformin is direct on the diseased cells or primarily indirect via the improvements in glucose and lipid metabolism, decreased insulin, and decreased inflammation.

6.2. Advancing clinical research on drug repurposing

The expanded indications for metformin have been studied and have been shown to have potential in diabetes, polycystic ovary syndrome (PCOS), cancer, and ageing. But the evidence is not the same in each of these areas. The cardiovascular effects of metformin remain to be confirmed, and the role of metformin in metabolic management for PCOS is relatively well established. The use of anti-cancer and anti-ageing properties is still in the early stages of development, moving from basic and observational evidence to more solid clinical proof.

Future clinical trials should, therefore, be large, multicenter, randomized, and double-blinded, placebo- or standard-treatment-controlled studies, when possible. Randomised controlled trials are more likely to equalise other factors such as body weight, severity of disease, lifestyle, other diseases, and other medications. This allows for the identification of whether or not metforminin gives any extra advantages. Important clinical endpoints, including cardiovascular death, heart attack, stroke, hospitalisation for heart failure, rather than biomarker measures like inflammation, blood lipids, or endothelial function should be assessed in studies for cardiovascular research.

In cancer research future studies should not just add cancer types together. Rather, they should target particular types of cancer, stages of disease and metabolism. For instance, researchers might consider whether metformin is more effective in cancer patients who have diabetes or high insulin levels, and whether it is more effective when used as part of chemotherapy, endocrine therapy, targeted therapy, or immunotherapy. Some cancers rely on the metabolism of mitochondria to a

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greater extent than others and targeting patients based on their metabolic characteristics may be more beneficial than targeting all cancer patients with metformin.

In anti-ageing research, study design should also move from single laboratory markers towards meaningful clinical outcomes. An example of this is the proposed study, called the Targeting Aging with Metformin Study (TAME). In development, rather than just lifespan, the proposed design will consider the ability to slow multiple age-related outcomes such as cardiovascular disease, cancer, cognitive decline, physical decline, and death.

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