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REVIEW

The function, mechanisms, and clinical applications of metformin: potential drug, unlimited potentials

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Abstract

Metformin has been used clinically for more than 60 years. As time goes by, more and more miraculous effects of metformin beyond the clinic have been discovered and discussed. In addition to the clinically approved hypoglycemic effect, it also has a positive metabolic regulation effect on the human body that cannot be ignored. Such as anti-cancer, anti-aging, brain repair, cardiovascular protection, gastrointestinal regulation, hair growth and inhibition of thyroid nodules, and other nonclinical effects. Metformin affects almost the entire body in the situation taking it over a long period, and the preventive effects of metformin in addition to treating diabetes are also beginning to be recommended in some guidelines. This review is mainly composed of four parts: the development history of metformin, the progress of clinical efficacy, the nonclinical efficacy of metformin, and the consideration and prospect of its application.

Keywords Metformin · Hypoglycemic · Cancer · Anti-aging · Repairing the brain

Introduction

With the rapid development of society, a high-pressure and rapid-paced life has become the norm. Many people would like to eat sweets to deal with the pressure they have. However, eating too much sugar can easily lead to some chronic diseases. For example, liver disease, cardio-cerebrovascular disease (hypertension, coronary heart disease, stroke, etc.), diabetes, malignant tumors, chronic obstructive pulmonary disease (chronic bronchitis, emphysema, etc.), mental abnormalities, psychosis, and so on (Lustig et al. 2012; Rippe and Angelopoulos 2016; Stanhope 2016; Sigala et al. 2021). They all have the characteristics of a long course, complex etiology, health damage, and serious social harm. Studies show that the number of adults with diabetes in China ranks first in the world, and it is even estimated that the number of adults with diabetes may reach 642 million in 2040. At the same time, diabetes tends to induce tumors and other diseases (Zhang et al. 2020b; Saleh et al. 2021), which means that diabetic patients often have more than one disease. Therefore, drugs that can simultaneously prevent or treat multiple concurrent diseases in diabetic patients are worthy of looking forward to (Zajda et al. 2020).

Years of research have shown that metformin, a first-line treatment for type 2 diabetes mellitus (T2DM), may be able to treat or prevent other complications in people with diabetes (Griffin et al. 2017; Jia et al. 2021; Schernthaner et al. 2022). Perhaps metformin could be the expected savior. Common chronic diseases such as cancer or tumor, cardiovascular disease, and organ disease can make diabetic patients uncomfortable, and the clinical efficacy of metformin found in clinical trials just corresponds to them (Fig. 1) (Kalmykova et al. 2019a;

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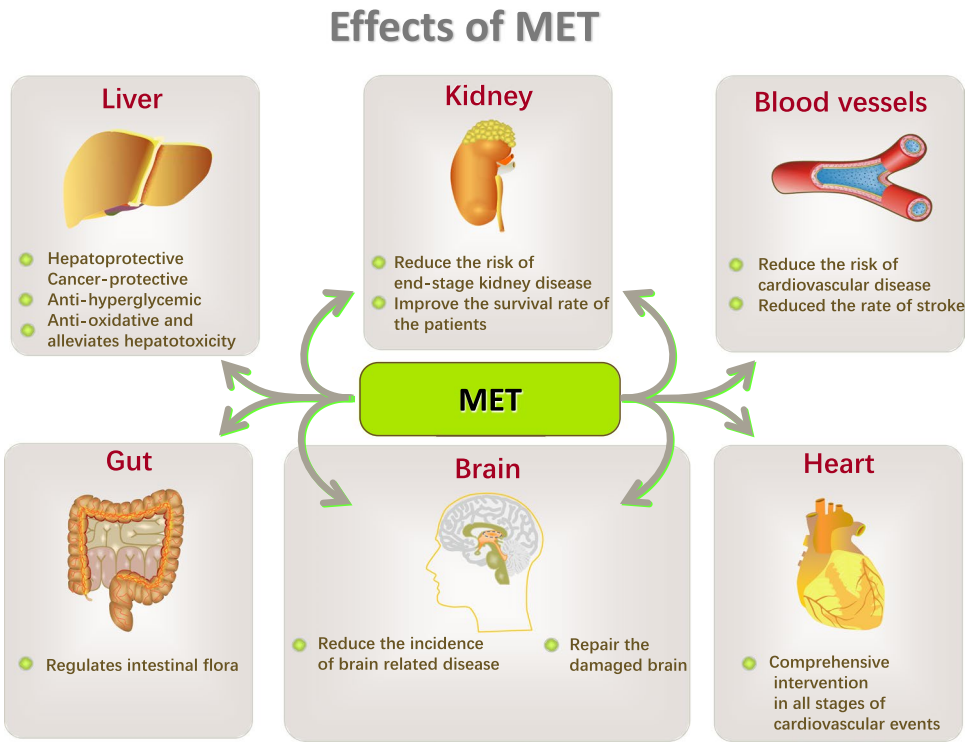

Fig. 1 Effects of metformin. Metformin has some effects on the liver, kidney, blood vessels, gut, brain, heart and so on, which can be applied to treat some cancer in those organs

Kalmykova et al. 2019b; Pugliese et al. 2019; Munoz et al. 2021; Zaccardi et al. 2021). To some extent, it is not too much to say that metformin is a lifesaver for people with diabetes or chronic diseases. However, most of the studies on the efficacy of metformin have not been validated by clinical trials. Most of the effects of metformin are expected, and the various magical therapeutic and preventive effects of metformin in clinical application still need further research and clinical validation.

Through data retrieval, the literature on metformin in anticancer, tumor inhibition, anti-aging, brain repair, cardiovascular protection, pulmonary inflammation inhibition, anxiety relief, anti-inflammatory, adjustment of intestinal flora, hair growth, and inhibition of thyroid nodules, prevention of stroke and other relevant studies was collected. According to the research results, the mechanism of action of the relevant efficacy was summarized, and the clinical application of metformin was predicted. This review is mainly composed of the historical development of metformin, its clinical curative effect, and its mechanisms and thinking, and looking forward to this review will focus on three parts around the various clinical efficacy of metformin and prevention mechanisms to carry on the summary. We would like to describe the current progress in investigating various clinical efficacy and preventive mechanisms of metformin in detail.

The history of metformin

Metformin is a precursor to the French Lilac, a medieval drug used to reduce polyuria and sugar in diabetics. During 1920–1950, due to the discovery of insulin and the toxic side effects of guanidine and its derivatives, guanidine glucose-lowering drugs (including metformin and metformin) temporarily faded out of people's sight. Metformin was first used in the clinical treatment of diabetes in 1957. Later, metformin was withdrawn from the market due to the side effects of lactic acidosis, thus confirming metformin as the only hypoglycemic drug that can reduce the complications of macrovascular and reduce the complications and mortality of T2DM. In 2000, metformin sustained-release tablets (Gvachin) were approved for sale in the United States, and some metformin drugs were developed in combination with other drugs. After that, metformin has been widely used and researched and has acquired a certain position in hypoglycemic drugs. In 2006, the American Diabetes Federation (ADA) and the European Diabetes Research Association (EASD) jointly issued a new consensus for the treatment of T2DM: newly diagnosed patients with T2DM should be treated with metformin—a first-line drug through the treatment process—along with lifestyle interventions (Fig. 2). Up to

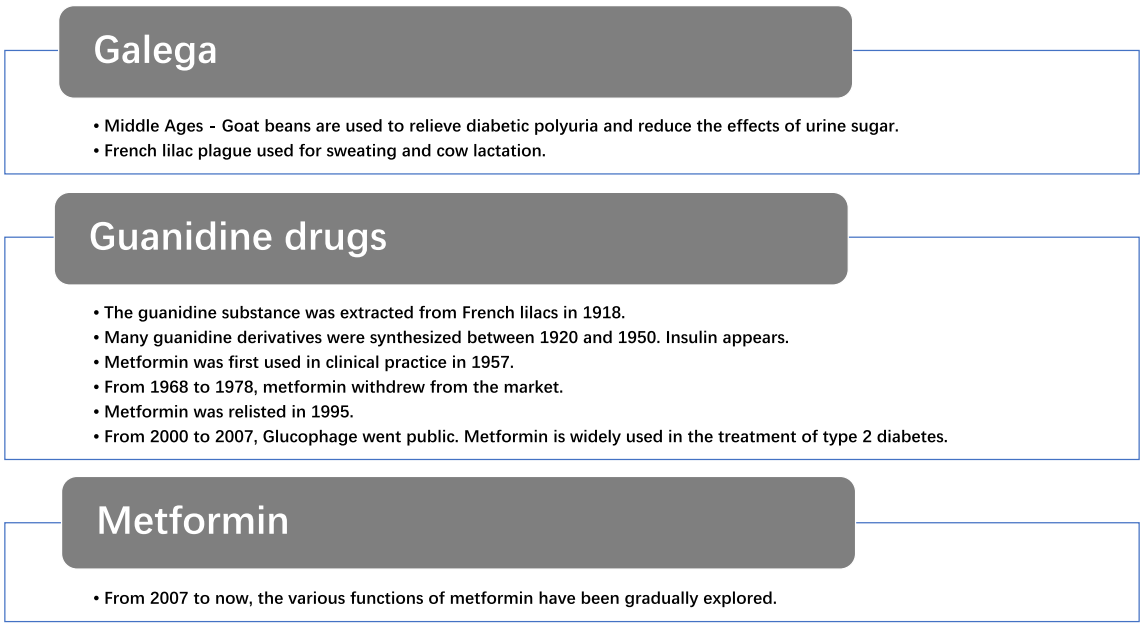

Fig. 2 The history of metformin. From Galega to metformin, it is a long history

now, many of metformin's special effects have yet to be clinically proven to play a role in disease treatment (Bailey 2017).

Clinical efficacy

Effect of lowering blood sugar and reducing weight

Metformin, as a drug to lower blood sugar (Moses 2010), can reduce the production of liver glycogen without increasing insulin levels in the body, inhibit the absorption of glucose in the intestinal tract and increase the uptake and utilization of glucose in the peripheral tissues, thereby increasing insulin sensitivity (Hausmann and Schubotz 1975; van Bommel et al. 2020). Metformin also can reduce the synthesis and storage of cholesterol and the level of blood triglyceride (TG) and total cholesterol. It does not cause hypoglycemia when taken alone, but should be treated with caution in combination with insulin or other oral hypoglycemic agents such as sulfonylureas and nateglinide (Flory and Lipska 2019). Studies have shown that long-term use of metformin can not only improve symptoms of hyperglycemia (Xu et al. 2019) but also contribute to weight loss in obese T2DM patients with a proper diet (low-glycemic diet or intermittent fasting) (Lee and Morley 1998; Masarwa et al. 2021). It can significantly reduce hyperglycemia and hyperlipidemia in patients with T2DM, and help to reduce the risk of some tumors. However, metformin cannot be taken as a weight loss drug alone, and so far no guidelines have been found to list it as a weight loss drug and recommend it.

How to inhibit glycogenosis in liver

Metformin can inhibit liver glycogenosis and reduce insulin resistance through the adenosine monophosphate-activated protein kinase (AMPK) signal transduction pathway (Musi et al. 2002; Wen et al. 2021) and inhibition of acetyl-CoA carboxylase (ACC), thus improving the sensitivity of surrounding tissues to insulin (Fig. 3A).

AMPK plays a key role in regulating cellular energy homeostasis (Zang et al. 2004; Banerjee et al. 2016). The liver metabolizes sugars mainly through the synthesis and decomposition of liver glycogen, as well as gluconeogenesis, to maintain the relative stability of blood glucose concentration. Metformin promotes the transfer of glucose transporters to the cell membranes of hepatocytes and increases the activity of insulin receptors in hepatocytes. Inhibition of fatty decomposition and TG degradation by brown fat cells reduced the level of free fatty acid (FFA) in blood. Experiments in mice showed that metformin inhibited inflammation caused by a high-fat diet (Coll et al. 2020). Metformin inhibits cellular fat accumulation in the liver and bone by activating the AMPK phosphorylation of ACC. Studies have confirmed that metformin can reduce the glucose output of the liver by 20–30% (Foretz et al. 2019). In the human body, brain blood cells, kidney medullary, intestinal, skin, and other tissues can use glucose without the help of insulin. Therefore, metformin can reduce the burden of insulin and

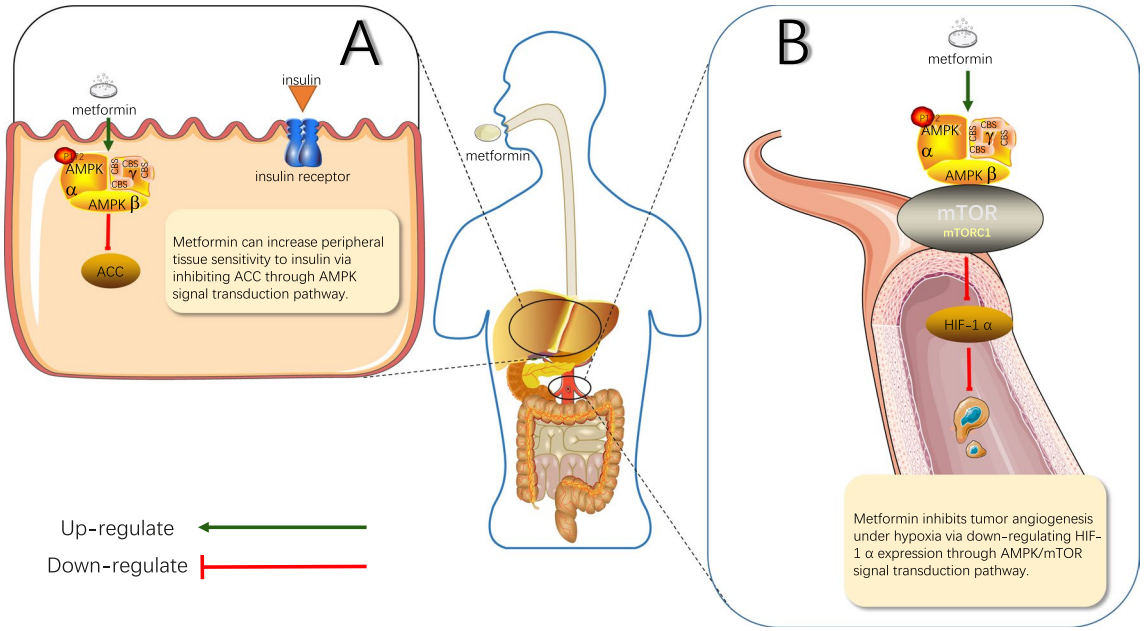

Fig. 3 Metformin works through the AMPK pathway. **A**. Metformin can increase peripheral tissue sensitivity to insulin via inhibiting ACC through the AMPK signal transduction pathway. **B**. Metformin inhibits tumor angiogenesis under hypoxia via down-regulating HIF-1 α expression through the AMPK/mTOR signal pathway

the effect of insulin resistance by increasing glucose utilization in insulin-independent tissues.

The mechanism of inhibition of gluconeogenesis independent of AMPK is mainly through the influence of energy, redox, cell membrane potential, and so on. Metformin can inhibit mitochondrial complex 1, reduce the production of ATP, and reduce the allosteric inhibition of ATP on key enzymes involved in glycolysis, therefore, increasing intrahepatic glycolysis. The decrease of ATP level in vivo will increase AMP's inhibition of the glucagon signaling pathway and inhibit gluconeogenesis induced by PKA activation. AMP can allosterically inhibit the key enzyme of gluconeogenesis, fructose-1, 6-bisphosphatase, and allosterically activate the key enzyme of glycolysis, phosphofructokinase, thereby inhibiting the process of glycerol and lactic acid to blood sugar. Metformin can promote the chloride outflow of hepatocytes and lead to the depolarization of cell membranes, thus reducing the uptake of gluconeogenic substrates (Foretz et al. 2019).

How to affect the absorption of sugar from the intestine

Studies have shown that metformin has a high concentration in the intestinal tract (Coll et al. 2020). By changing the structure and diversity of intestinal microbiota, metformin can restore the proportion of intestinal microbiota, increase the probiotics of intestinal microbiota (such as Blautia SPP and Faecali bacterium SPP.), enhance the ability of bacteria to produce special types of short-chain fatty acids, inhibit glucose absorption (Bybel et al. 2011; de la Cuesta-Zuluaga et al. 2017; Zhang et al. 2020a), thus playing a role of lowering blood sugar and positively regulating the immune system.

How does metformin reduce appetite and weight loss?

Gregory R. Steinberg's team found that metformin upraised the growth differentiation factor (GDF15) in the body without using the AMPK pathway. Metformin can upregulate GDF15 in vivo without the AMPK pathway. Metformin over-regulates the transcription factors activating transcription factor 4 (ATF4) and C/EBP-homologous protein (CHOP) upstream of GDF15 to increase the secretion of GDF15 in hepatocytes, achieve weight loss by suppressing appetite, increase satiety and reduce hunger (Duan et al. 2013; Kim et al. 2013; Calco et al. 2021). The highly expressed GDF15 in the liver interacts with the glial cell-derived neurotrophic factor (GDNF) family receptor-like (GFRAL) receptor in the posterior brain to inhibit appetite for high-fat foods and regulate body weight and energy balance. This study demonstrates the potential value of GDF-15 in the study of metformin for weight loss (Fig. 4).

Anticancer/tumor effects

Metformin has several anticancer mechanisms and may be used to prevent many types of cancer, while combination drugs may enhance its anticancer effect (Chen et al. 2021c;

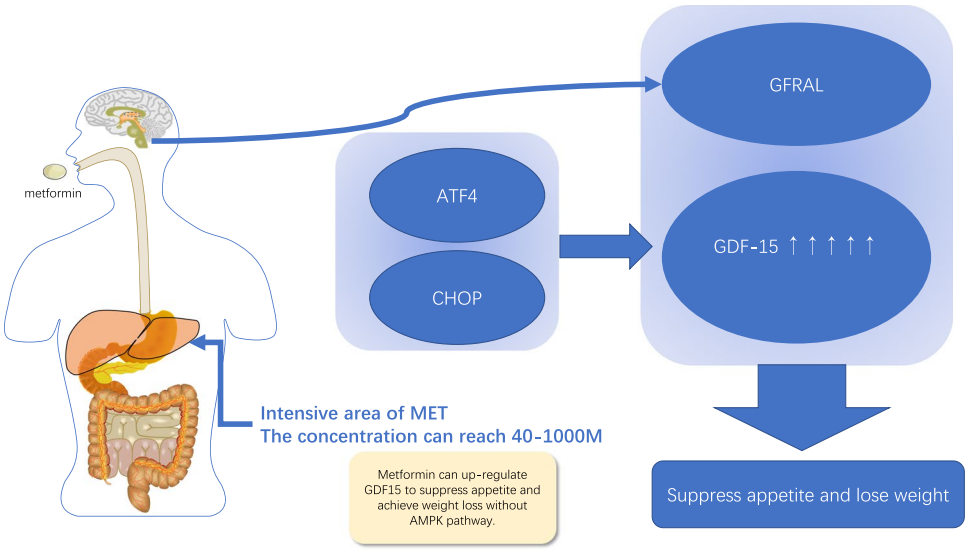

Fig. 4 Metformin can up-regulate the growth differentiation factor (GDF15) in the body. The up-regulation of GDF15 can suppress appetite to lose weight

Misirkic Marjanovic et al. 2021; Xia et al. 2021). It may have a direct inhibitory effect on individual cancers and this anticancer therapeutic effect may have a significant impact on the quality of human life. In summary, metformin can reduce the risk of tumors in patients with T2DM. However, the specific mechanism of metformin's tumor inhibition is not yet clear, and most of the studies are only at the experimental stage. Metformin has great potential in anticancer treatment.

Intermittent fasting combined with oral administration of metformin inhibits tumor growth and reduces the risk of developing tumors in patients with T2DM because tumors are sensitive to metformin in low-glucose conditions. Metformin can reduce the level of myeloid cell leukemia-1 (MCL-1) by activating protein phosphatase 2A (PP2A) and glycogen synthase kinase 3β (GSK3β) and cancerous inhibitor of PP2A (CIP2A) [CIP2A are highly expressed in a variety of tumors, and inhibit the activity level of PP2A] to inhibit tumor growth (Elgendy et al. 2019). In addition, hypoxia-inducible factor-1 α (HIF-1α), which controls oxygen change and regulates cell function, and is an important factor for tumor cells to adapt to the hypoxia environment, is expected to be a target for tumor therapy. Finally, the expression of HIF-1α is inhibited through the AMPK/mTOR signal transduction pathway, and the formation of tumor neovascularization under hypoxia is inhibited, thus inhibiting tumorigenesis (Fig. 3B) (Palazon et al. 2017).

Meta-analysis showed that metformin can reduce the incidence of cancers and increase the survival time of T2DM patients with cancers (Coyle et al. 2016). The specific mechanism has not been determined, but there are many speculations and possible tumor inhibition pathways.

Metformin may inhibit the reduction of CD8+tumor-infiltrating lymphocytes (TILs) due to apoptosis by increasing the number of CD8+TILs in tumors, thereby taking an anticancer effect (Fig. 5A) (Kim et al. 2020). Metformin may indirectly play an anti-cancer role in reducing the growth stimulation effect on tumor cells via lowering the levels of insulin/insulin-like growth factor-1 (IGF-1) and serum insulin (Fig. 5B) (Sarmento-Cabral et al. 2017; Chen et al. 2021b). It is possible to induce the inhibition of mammalian target rapamycin complex 1 (mTORC1), thereby inhibiting the drug resistance and proliferation of tumor cells and activating autophagy to promote the apoptosis of tumor cells (Fig. 5C). This process can be achieved by either AMPK or non-AMPK—dependent pathways. It may also increase the number of memory T cells, promote the apoptosis of cancer cells, and enhance the antitumor function of T cells by inhibiting the signal transmission of mTORC1 (Mossmann et al. 2018). It can inhibit tumor micro-environmental immunosuppression, and inhibit the differentiation of macrophages to prevent tumor metastasis. Programmed cell Death 1 Ligand 1 (PD-L1) inhibits the expression of PD-L1 in the cancer cell. Metformin can reduce the stability and membrane localization of PD-L1 through the degradation of related proteins in cancer cells, and prevent the expression of PD-L1 in cancer cells (Fig. 5D) (Soliman et al. 2020). It is also possible to inhibit the activity of the transcription factor NF-KB signaling pathway by activating AMPK (killing liver cancer cells and inhibiting tumor growth) (Fig. 5E) (Xu et al. 2017). The expression of Kruppel Like Factor 5 (KLF5) can also be down-regulated by inhibiting PKA, and the proportion of rods in HCC1806 and HCC1937 cell lines and the number of microspheres formed by cell lines can also be reduced to inhibit the stem cells of cancer cells (Fig. 5F).

Triple-negative breast cancer (TNBC)

TNBC is the most difficult of the four types of breast cancer to cure and the one with the worst prognosis. It is most

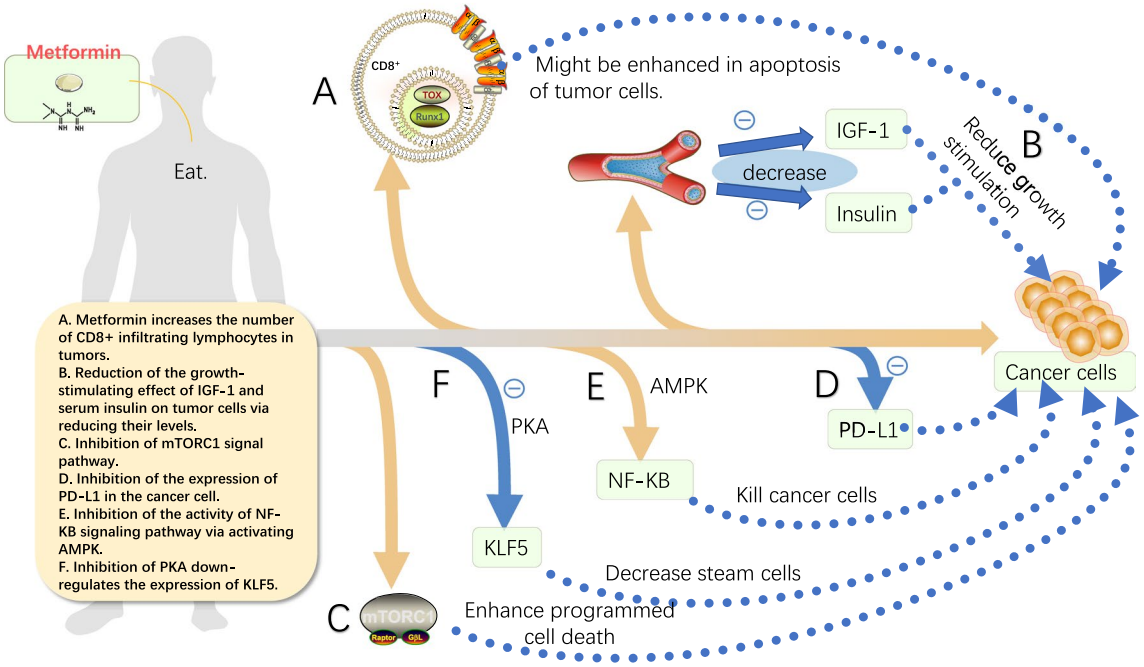

Fig. 5 Antitumor mechanisms of metformin. **A**. Metformin may increase the number of CD8 + infiltrating lymphocytes (TILs) in tumors. **B**. Metformin lowers the levels of IGF 1 and serum insulin to reduce their stimulatory effects on the growth of tumor cells. **C**. Metformin inhibits tumor microenvironment immunosuppression and prevents tumor metastasis via inhibiting the mTORC1 signal pathway. **D**. Metformin reduces the stability and membrane localization of PD-L1 by degrading related proteins in cancer cells, thereby preventing PD-L1 expression in cancer cells. **E**. Metformin inhibits the activity of the NF-KB signaling pathway via activating AMPK. **F**. Metformin inhibits PKA to down-regulate the expression of KLF5

common in young women. Although TNBC has a poor prognosis and a higher risk of death, most TNBCs are treated with chemotherapy. The therapeutic targets of TNBC have always been a difficult problem in clinical treatment (Li et al. 2021a). Triple-negative refers to the three targets mainly targeted in treatment: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor (HER).

The scientists were surprised to find that the combination of metformin and heme significantly inhibited TNBC tumor growth. BTB and CNC Homology 1 (BACH1), an anti-cancer target transcription factor of heme, is a key factor regulating mitochondrial metabolism and is essential for cancer metastasis. However, inhibition of BACH1 expression has no significant side effects on normal cells, so BACH1 can be used as a therapeutic target for cancer. Heme can degrade the BACH1 protein in cancer cells, forcing them to change their metabolic pathways (from anaerobic respiration to aerobic respiration). BACH1 inhibits the transcription of mitochondrial electron transport chain (ETC) genes directly and regulates pyruvate dehydrogenase kinase (PDK) directly. BACH1 phosphorylates PDH Ser293 to inhibit its activity and enhance the tricarboxylic acid cycle metabolism, which is a key regulator of glycolysis and aerobic respiration metabolism. Metformin, as a low-toxicity ETC inhibitor, can inhibit the aerobic metabolism of cancer cell mitochondria, and the combination of the two drugs can more significantly inhibit the growth of TNBC tumor cells than the two alone (Fig. 6) (Wahdan-Alaswad et al. 2014; Shi et al. 2017; Strekalova et al. 2017; Liu et al. 2021).

In addition, metformin combination therapy is promising for breast cancer – a triple therapy of metformin + Venetoclax + PD-1 antibody may be available for breast cancer (Bayraktar et al. 2012; Lee et al. 2019; Varghese et al. 2019). The treatment has been approved by the Food and Drug Administration as a first-line treatment for TNBC. Venetoclax is the world's first Bcl-2 inhibitor, primarily used to treat leukemia. It can inactivate the Bcl-2 protein, which can inhibit the apoptosis of cancer cells, restart the suicide program of cancer cells, and destroy "the immortal legend of cancer cells" (Wahdan-Alaswad et al. 2016; Wang et al. 2020a). Metformin combined with Venetoclax activates MCL cells, while PD-1 antibody (Tecentriq) and Abraxane (albumin paclitaxel) maintain MCL cells for longer periods, perhaps prolonging survival in cancer patients. However, it has been found that adding metformin to standardized breast cancer treatment does not significantly improve survival in patients without diabetes (Goodwin et al. 2022). Therefore, whether metformin should be used in all breast cancer patients is controversial and needs further validation.

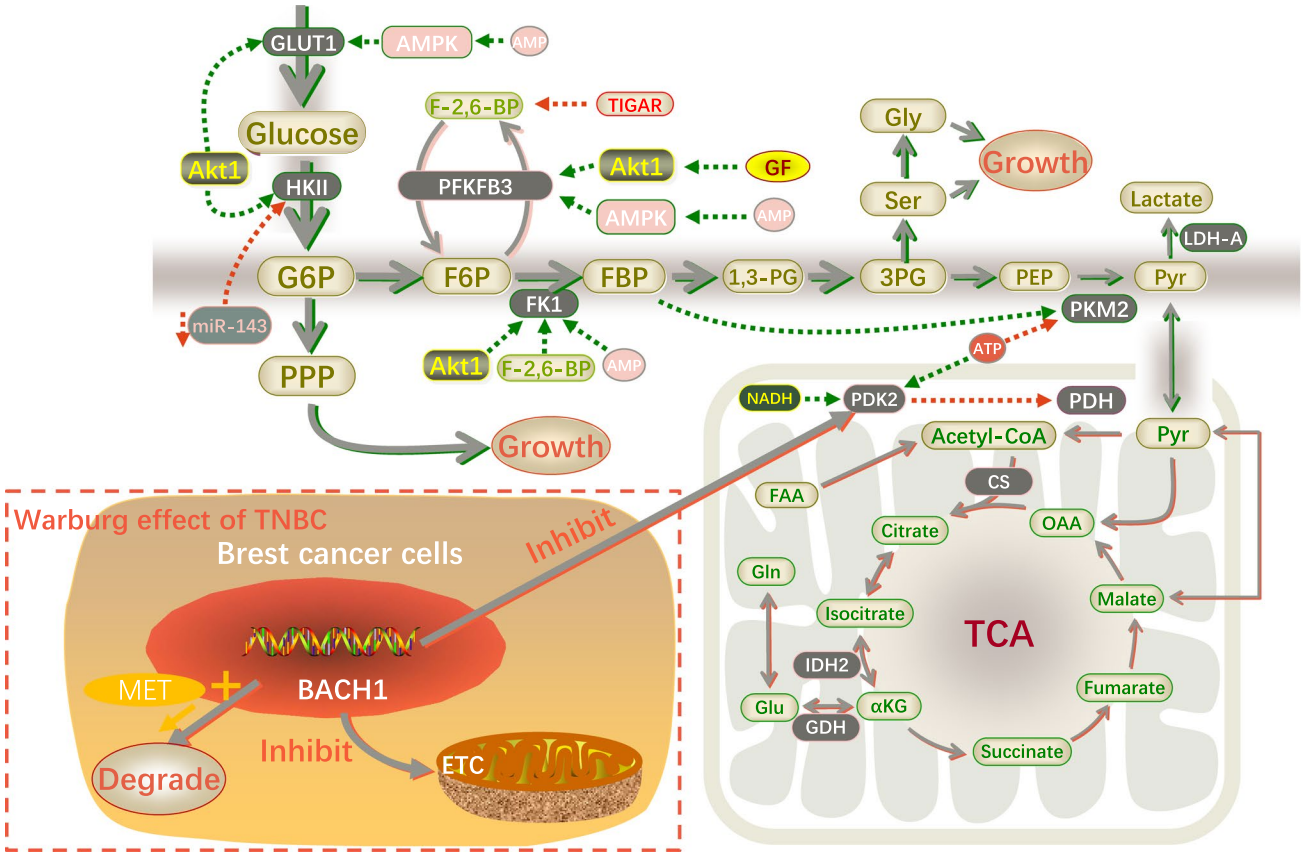

Fig. 6 Effects of metformin on mitochondrial metabolism. Metformin can inhibit the aerobic metabolism of mitochondria of cancer cells and heme can inhibit the regulation of BACH1 on aerobic respiration, which directly inhibits the transcription of the mitochondrial ETC (electron transport chain) gene. The combination of heme and metformin can significantly inhibit the growth of TNBC tumor cells

Cancers that are nischarin deficient

Protein Nischarin participates in a variety of biological reactions in vivo and plays an important role in inhibiting tumor migration and tumor cell invasion. Research by Dr. Suresh Alahari et al. has found that interfering with Nischarin may promote breast tumor growth and inhibit AMPK activation (Gollavilli et al. 2015). However, with metformin treatment, the above conditions can be reversed under Nischarin's absence. Therefore, for cancers lacking the Nischarin protein, it is possible to inhibit the occurrence of cancer by activating the AMPK function. There is still much room for research on the specific mechanism of metformin acting on breast cancer cells (Dong et al. 2020). Activation of AMPK prevents the Nischarin gene from enhancing tumor growth and metastasis, which can be used to treat malignant diseases.

Effect on hepatobiliary tumor/hepatobiliary cancer

Surgical resection is the main treatment for intrahepatic cholangiocarcinoma (ICC). Studies have found that in hepatobiliary cancer/hepatobiliary tumors, the abnormal FGF19-FGFR4 signaling pathway is an important factor causing cancer, and fibroblast growth factor receptor (FGFR) inhibitory therapy may be a new target for cancer treatment to resist HCC/ICC (Chen et al. 2021a).

Metformin combined with arsenic trioxide (ATO) may inhibit ICC through conventional chemotherapy (Ling et al. 2017). By promoting apoptosis, inducing G0/G1 cell cycle arrest, increasing intracellular reactive oxygen species (ROS) synergistic inhibition of ICC cell proliferation, and so on, they effectively reduced ICC growth in the ICC xenograft model but failed to increase the survival rate (Chaiteerakij et al. 2013; Kaewpitoon et al. 2015; Yang et al. 2016; Trinh et al. 2017; Di Matteo et al. 2021). In diabetics, metformin reduced the risk of ICC by 60 percent. In addition, metformin can effectively enhance the sensitivity of ICC cells to chemotherapy drugs such as sorafenib 5-fluorouracil ATO. Metformin combined with conventional chemotherapy can improve efficacy. It may be that metformin inhibits ICC by regulating the AMPK/P38 MAPK ERK3/mTORC1 pathway and enhancing ATO sensitivity (Ling et al. 2017).

In the liver, adiponectin secreted by fat cells is involved in the control of body metabolism. Perhaps adiponectin combined with metformin can be used as a new treatment for liver cancer, whose efficacy and mechanism remain to be verified. Murff et al. found that T2DM patients taking metformin were less likely to develop liver cancer (Murff et al. 2018). Metformin inhibits the activity of the transcription factor NF-KB signaling pathway by activating AMPK. This study revealed that metformin has great potential in the treatment of hepatocellular carcinoma.

Esophageal cancer

Esophageal cancer is the second largest gastrointestinal tumor after gastric cancer (Siegel et al. 2022). Studies have shown that metformin at a normal dose can selectively inhibit the growth of esophageal squamous cell cancer cells, induce apoptotic cell death, inhibit cell proliferation and induce autophagy (Wang et al. 2020b). The induction of autophagy was discovered by scientists through the establishment of a 4-Nitroquinoline N-oxide (4NQO) -induced mouse model of esophageal squamous cell carcinoma. Metformin can enhance the phagocytic function of esophageal squamous cell carcinoma at a low dose. Metformin changes the tumor microenvironment of esophageal squamous cell carcinoma cells and thus has the effect of inhibiting tumor growth. Metformin may activate STAT3 and increase AMPK content in immune cells by changing the cytokine secretion profile of immune cells, thus inactivating the STAT3 network signaling pathway (especially the STAT3-BCL2-Beclin1 network signaling pathway) to promote cross-talk between apoptosis and autophagy and achieve the purpose of inhibiting tumor growth. Studies have shown that metformin can not only accelerate the differentiation of gastric stem cells into gastric acid-producing gastric wall cells, but also increase the number to regulate the secretion of gastric acid in the stomach and greatly reduce the risk of gastric cancer in people infected with Helicobacter pylori, but also reduce the risk of rectal cancer (Zell et al. 2020; Lu et al. 2021a).

Head and neck cancer

Some studies have shown that metformin may eliminate the stem cell characteristics of head and neck cancer cells and prevent cancer cells from becoming malignant (Crist et al. 2022). It can be used to prevent high-risk cancer populations from cancer. Metformin blocks cancer cell metabolism by inhibiting the mitochondrial complex of cancer cells to reduce the expression of cancer stem cell programs. And metformin triggers the differentiation of cancer cells, directly acting on the head and neck cancer initiation cells.

Pancreatic cancer

Diabetes mellitus can increase the risk of pancreatic cancer and is a high-risk factor for pancreatic cancer. Some research suggests that metformin may reduce the risk of pancreatic cancer in diabetics. Bodmer et al. found that the odds ratio of pancreatic cancer was 0.43 (95%CI 0.23–0.80) in women with diabetes who took metformin for a long period compared with those who did not take the drug. However, long-term insulin or sulfonylureas use had a ratio of 1.90 for pancreatic cancer compared with non-users (Bodmer et al. 2012). Inhibition of the signaling pathway of the pancreatic stellate cell (PSC) used to synthesize hyaluronic acid and type 1 collagen also prevents the recruitment of tumor-related macrophages. Chen et al. showed reduced pancreatic acinar-ductal metaplasia and pancreatic intraepithelial neoplasia in mice treated with metformin. Metformin can inhibit tumor proliferation and metastasis and inhibit the transformation from chronic pancreatitis to pancreatic cancer (Chen et al. 2017).

Lung cancer

Previous studies have suggested that metformin plays an anticancer role primarily by AMPK and inhibiting protein synthesis (Wang et al. 2013; Lu et al. 2021b). Meta-analysis showed that metformin could reduce the risk of lung cancer in patients with T2DM and improve the survival rate, and its protective effect on patients in Asia was clear, so it was promising to be used in the treatment of patients with T2DM complicated with lung cancer (Gupta et al. 2018). The roles of metformin in prolonging the life cycle of patients with advanced lung cancer with epidermal growth factor receptor (EGFR) mutations and benefiting non-small cell cancer patients remain controversial (Salani et al. 2012; Ko et al. 2020).

Effects on the brain

Repair the brain

Metformin has great potential in promoting brain-damaged and episodic cognitive recovery and brain repair and growth. A related study conducted at the University of Toronto involved both human patients and animal models. Metformin promoted the formation of new neurons in the forebrain and hippocampus dentate Gyrus in animals after brain injury, which promoted brain nerve growth and enhanced cognition and memory (Hwang et al. 2010; Ng et al. 2014; Zhu et al. 2020). Previous animal studies have shown that metformin selectively activates neural stem cells in adult female mice to repair the brain and restore cognitive function (Kuan et al. 2017; Mandwie et al. 2021). Metformin, on the other hand,

has been shown in clinical trials to help repair the brains of patients with neurological disease, saving a radiation-induced decline in the neural stem cell pool (no gender difference, but more significant in women) (Ayoub et al. 2020; Yuen et al. 2021). This study provides a credible basis for the treatment of metformin to repair the brain. Metformin, in the presence of estrogen (mainly estrogen estradiol), activates neural stem cells in the brain and improves brain function. The aPKC (atypical protein kinase C)-CBP (cAMP-response element binding protein) pathway is an important pathway mediating the directional differentiation of neural stem cells into mature neurons. Metformin may activate the aPKC-CBP pathways in hepatocytes and promote neuron regeneration in rodents and humans (Wang et al. 2012).

Reduce the risk of dementia

Metformin has the potential to reduce the risk of vascular events and vascular dementia (Lin et al. 2018b; Ma et al. 2021). It may be related to metformin-reducing systemic inflammation (Lin et al. 2018a; Li et al. 2021b; Xiong et al. 2021). This may be good news for many middle-aged and elderly patients with T2DM. Using metformin for a long time may help them avoid the trouble of Alzheimer's disease and save a lot of burden for their families.

Relieve anxiety

Anxiety disorder is one of the greatest psychological problems in today's society. Proper anxiety might make people work more efficiently, while excessive anxiety tends to make people sick, not only physically unhappy, but also makes them less happy in life, negatively affects the people around them, and so on. It has been found that metformin may be used to treat some forms of autism, such as fragile X syndrome, metabolic or psychiatric disorders, or depression. By reducing the content of branched-chain amino acids in the diet, it was speculated that the experiment also achieved the effect of reducing the anxious behavior of male mice (Fan et al. 2019). Metformin may reduce anxiety-like behavior in male mice by lowering the levels of circulating branched-chain amino acids, increasing the availability of serotonin in the brain, and improving neurotransmission in the hippocampus (Zemdegs et al. 2019).

Cardiovascular diseases

Preclinical and clinical studies have shown that metformin is directly anti-inflammatory through AMPK-dependent or independent inhibition of nuclear transcription factor B (NFκB) (Ba et al. 2019). Perhaps metformin can improve chronic inflammation by improving metabolic parameters such as hyperglycemia, insulin resistance, and dyslipidemia, which leads to atherosclerosis (Li et al. 2009; Feng et al. 2021; Seneviratne et al. 2021). Consequently, it has a direct anti-inflammatory effect.

Reduce the risk of cardiovascular diseases

Studies have shown that taking metformin can reverse heart damage in people without diabetes (Mohan et al. 2019). T2DM patients taking metformin had a relatively low risk of cardiovascular disease, mortality from varicose veins, T2DM venous thromboembolism (VTE), and hospitalization for heart failure. Therefore, we inferred that metformin has a cardiovascular protective effect. Metformin reduces the risk of heart attacks and stroke by reducing inflammation in the lungs that cause clotting caused by air pollution. Metformin can also prevent inflammation caused by smog, prevent immune cells from releasing a dangerous molecule into the blood, inhibit the formation of arterial thrombosis, and thus reduce the risk of cardiovascular disease by reducing the excessive production of dicarbonyl (Beisswenger et al. 1999), which may improve cardiac autonomic nerve function in this population.

Metformin can also intervene in all stages of the chain of cardiovascular events: Reduce the risk factors of cardiovascular disease (weight loss, insulin resistance, blood pressure reduction, blood lipid improvement, anticoagulation, etc.) and exert cardiovascular protective effects (He et al. 2021). It can directly improve vascular endothelial function. It can reduce the formation of atherosclerosis, reduce myocardial hypertrophy myocardial infarction, and heart failure; Long-term treatment can improve cardiovascular outcomes in patients with T2DM, metformin can improve endothelial function, and reduce the level of endothelial function markers such as von Willebrand factor (vWF) soluble vascular adhesion molecule-1 (SVCAM-1) and plasminogen activator inhibitor-1 (PAI-1) (Fidan et al. 2011; Ding et al. 2021). Metformin can reduce the size of acute myocardial infarction and improve the absence of reflow after angioplasty of acute myocardial infarction. A retrospective study has shown that long-term application of metformin can significantly reduce the level of creatine kinase (CK) creatine kinase isoenzyme (CK-MB) troponin T in patients and reduce myocardial infarction area (Eppinga et al. 2017; Thein et al. 2020; Sardu et al. 2021). The cardiovascular effects of metformin also reduced the risk of stroke in patients with diabetes who received metformin compared to those who did not (Westphal et al. 2020; Zemgulyte et al. 2021).

Aortic aneurysm

Studies have shown that metformin is negatively correlated with aortic aneurysm development, and a randomized double-blind trial is still needed to verify that metformin

may also reduce the probability of aortic disease and related events (Han et al. 2019; Thanigaimani et al. 2021) which effectively reduce the risk of atherosclerosis (ASCVD) in T2DM patients.

Type 1 diabetes (T1DM)

Studies have shown that metformin can also improve endothelial function, insulin sensitivity, and vascular health, and improve cardiovascular risk in patients with T1DM, which is expected to achieve cardiovascular benefits (Liu et al. 2020). Metformin treatment independently increased levels of the oxidative stress marker prostaglandin F2 (PGF2) and improved flow-mediated dilation (FMD) in patients with type 1 diabetes mellitus. Metformin may improve atherosclerosis and reduce myocardial injury by improving cardiovascular risk factors, and other mechanisms have cardiovascular protective effects (Snell-Bergeon 2017).

Anti-aging

Clinical trials in the United States have found that metformin may increase health and prolong life (Podhorecka et al. 2017; Kumari et al. 2021). Studies have found that the anti-aging effect of metformin is related to the effect of its metabolites, guanidine, and dietary intake on the intestinal microbiome through a high-throughput quadrate screening method that integrates the four major elements of the host microbiome, drug-nutrition (Piskovatska et al. 2019). There have also been studies using cocktails of growth hormones and dehydroepiandrosterone (DHEA) and metformin to regenerate the thymus in users, reducing biological age (Torres et al. 2020). Metformin can directly inhibit the activity of many enzymes involved in ATP synthesis and decomposition by activating AMPK, thus reducing energy consumption. It is also possible to increase mitochondrial biosynthesis by modulating the peroxisome proliferator-activated receptor (PPAR) co-activator. Activation of AMPK also increases autophagy in the body (Ma et al. 2022). Metformin may inhibit mTOR. Inhibited mTORC1 increases ACAD10 transcription through SKN-1/Nrf2. ACAD10 may be related to some proteins that affect the growth and development of the body and the functions of ribosomes and mitochondria. Metformin may regulate the IGF-1 signaling pathway to reduce the patient's blood glucose levels, slow down body aging, and extend life. Metformin may inhibit electron transport chain complex 1 by reducing ROS production to reduce the number of electron transfers and prevent electron transfer, reduce the production of ROS, and reduce the cumulative damage of DNA, to achieve the anti-aging effect. Metformin may regulate sirtuin (SIRT) expression to prolong life: a variety of SIRT may regulate mitochondrial function and affect lifespan (Glossmann and Lutz 2019).

The lungs

Metformin has been shown to protect against lung cancer (Xiao et al. 2020; Lu et al. 2021b), improve the prognosis of lung cancer patients, and prevent pulmonary inflammation caused by haze. It can relieve allergic eosinophilic airway inflammation in obese mice. It reduces the risk of lung disease in non-smokers and increases the risk of lung disease in smokers. A team led by Professor Scott Budinger found metformin prevented inflammation caused by smog in mice (Soberanes et al. 2019). It prevents immune cells from releasing a dangerous molecule into the bloodstream, which inhibits the formation of arterial clots and thus reduces the risk of cardiovascular disease.

Pulmonary idiopathic pulmonary fibrosis

Studies have shown that metformin can reverse pulmonary fibrosis in mice. Metformin showed significant antifibrosis effects (Kheirollahi et al. 2019; Gu et al. 2021). Metformin plays an effective anti-fibrotic role by regulating metabolic pathways and inhibiting the effect of transforming growth factor 1 (TGF 1) on collagen formation, activating PPARγ signaling, and inducing adipogenic differentiation in lung fibroblasts.

Asthma

The study has shown that metformin can relieve allergic eosinophilic airway inflammation in obese mice (Guo et al. 2021). The study also found that metformin significantly reduced the incidence of asthma attacks and hospitalizations in patients with asthma, and was closely associated with survival benefits in patients with COPD and diabetes. Metformin may relieve allergic eosinophilic airway inflammation and restore normal eosinophilic and tumor necrosis factor (TNF-A) levels in bronchoalveolar lavage and lung AMPK levels. Asthma can be alleviated by inhibiting airway smooth muscle cell proliferation through AMPK-dependent channels.

Assist in smoking cessation

The study found that long-term smoking in patients led to the activation of the AMPK signaling pathway, which was inhibited when nicotine withdrawal occurred. Therefore, it is speculated that activating the AMPK signaling pathway with drugs may alleviate the withdrawal response. Tests on mice have found that metformin relieves nicotine

withdrawal symptoms in mice and may be used to quit smoking (Kaisar et al. 2017).

Ovary and uterus

Polycystic ovary syndrome (PCOS)

Tests in the 1990s showed that metformin restored ovulation function and improved PCOS (hyperandrogenism) by reducing insulin resistance (Tariq et al. 2007). AlHussain et al. found that metformin increases the live birth rate of clinical pregnancy and reduces anxiety in patients with PCOS (AlHussain et al. 2020). Another meta-analysis suggests that metformin may be considered in combination therapy for women with PCOS who have undergone in vitro fertilization or intracytoplasmic sperm injection and embryo transfer (IVF/ICSI-ET) cycles (Wu et al. 2020).

Gestational diabetes mellitus (GDM)

Data have shown that metformin has the same hypoglycemic effect on GDM as glibenzoide, and short-term use of metformin is safer, while long-term use of metformin has an impact on offspring (Bashir et al. 2020). This may increase the risk of obesity in offspring. Compared with glibenzoide, metformin was more inefficient in the treatment of GDM patients, and it could not reduce maternal triglyceride levels (Balsells et al. 2015).

Hair

Some studies have shown that metformin topical application may be used to treat hair loss during remanence, which stimulates the hair follicles of mice from remanence to growth and promotes hair growth (Araoye et al. 2020; Sun et al. 2021). However, there has been a reported case of acute hair loss in a woman with PCOS who took metformin (Rezvanian et al. 2009).

Hepatorenal

Metformin has been shown to reduce the risk of death (Crowley et al. 2017) and end-stage kidney disease (ESRD) in patients with T2DM who have developed cirrhosis of the liver or chronic kidney disease (CKD) with impaired renal function. Improve the risk of death from renal failure and kidney disease but be alert to the risk of lactic acidosis (Borbely 2016). Large studies have shown that metformin in patients with T2DM with CKD is associated with a reduced risk of death and ESRD without an increased risk of lactic acidosis, suggesting that metformin may reduce the risk of death from renal failure and kidney disease (Bakris and Molitch 2016; Gosmanov et al. 2021).

Thyroid

It has been found that metformin reduces thyroid volume and reduces the occurrence of goiter and thyroid nodules. In addition, studies have shown that metformin can treat thyroid nodules (Krysiak et al. 2015; He et al. 2019). Metformin can inhibit the growth of thyroid cells and different types of thyroid cancer cells by affecting the insulin/IGF1 and mTOR pathways. Furthermore, it is possible to enhance the role of thyroid hormone in the pituitary and adenosine by activating AMPK, thereby reducing fluctuations in thyroid stimulating hormone (TSH) levels in diabetic patients. Thyroid nodules can be treated by regulating the signal transduction pathway between TSH and IGF-1.

Prevention of stroke

Long-term studies have shown a sustained reduction in diabetes risk with metformin, showing the potential to prevent trends in cancer and stroke, and have expanded and updated the results including microvascular complications, cardiovascular events, cancer incidence, and the influence of age (Westphal et al. 2020). Age had a greater effect on the risk of kidney disease among all interventions. Metformin's ability to prevent stroke was more significant in people with higher baseline blood glucose levels and women with a history of GDM.

Thinking and perspectives

The clinical application prospect of metformin is infinite. Here, we summarize clinical trials involving metformin (Table 1). If we can prove the mechanism of its various curative effects, it will achieve certain breakthroughs in cancer treatment, anti-aging treatment, brain repair treatment, and other aspects, and improve the quality of human life. Due to the numerous clinical effects of metformin, the mechanism of action of each of its therapeutic effects may be related. If we want to investigate the mechanism of action of metformin, maybe we can start from the whole, link up the mechanism of action of each therapeutic effect, and study a series of influencing factors.

The clinical efficacy of metformin in various treatments is still controversial and needs more clinical and experimental support. Starting from the therapeutic effect of diabetes, exploring the mechanism of metformin's other effects may be able to develop into another new field. Combined treatment with metformin may be able to enhance the efficacy and achieve the multiplying effect. To sum up, there is a lot of room for research on cancer and anti-aging.

Table 1 Some clinical trial results and existing problems of metformin in recent years

Field	Research	Issue	Outcome	Expectation	Reference
Aging	Reversal of epigenetic aging and immunosenescent trends in humans	Whether metformin can promote thymus regeneration	The participants' biological age was reduced by an average of 2.5 years	Further large sample size studies are needed to verify the anti-aging effect of metformin	(Fahy et al. 2019)
Abortion and premature delivery	Use of metformin to treat pregnant women with polycystic ovary syndrome (PregMet2): a randomised, double-blind, placebo-controlled trial	Whether metformin reduces the risk of miscarriage and preterm birth in women with polycystic ovary syndrome	Metformin significantly reduces the risk of miscarriage and preterm birth in women with polycystic ovary syndrome, but has no effect on gestational diabetes	Further research is needed to clarify why metformin has no effect on gestational diabetes	(Lovvik et al. 2019)
Cancer	Metformin selectively inhibits metastatic colorectal cancer with the KRAS mutation by intracellular accumulation through silencing MATE1	Metformin as a potential new antitumor drug, its therapeutic effect is controversial	Combined with metformin can significantly prolong the median survival time of colorectal cancer patients on the basis of standard antitumor therapy	More studies are needed to test metformin in other tumors	(Xie et al. 2020)
Cardiovascular Benefits	Clinical Outcomes With Metformin and Sulfonylurea Therapies Among Patients With Heart Failure and Diabetes	The effect of metformin on cardiovascular risk may vary with differences in ejection fraction	Metformin can improve the clinical outcome of elderly diabetic patients with ejection fraction > 40%	Larger sample size studies are needed to confirm that patients with ejection fraction > 40% benefit from metformin	(Khan et al. 2022)
Cognitive decline	Metformin Use Is Associated With Slowed Cognitive Decline and Reduced Incident Dementia in Older Adults With Type 2 Diabetes: The Sydney Memory and Ageing Study	The effect of metformin on dementia risk has been controversial, with the possibility that it may be associated with both an increased and a reduced rate of dementia	Metformin has been linked to reduced cognitive decline in older adults with type 2 diabetes	Trials are needed in both diabetic and non-diabetic patients to see if metformin is associated with remission of cognitive decline	(Samaras et al. 2020)
Inflammatory	Association Between Preoperative Metformin Exposure and Postoperative Outcomes in Adults With Type 2 Diabetes	Adults with comorbidity tend to have higher rates of postoperative mortality and readmission after major surgical intervention	Those who took metformin before surgery had lower levels of inflammation and a 28 percent lower relative risk of death 90 days after surgery, and a 16 percent lower relative risk of readmission within 30 days and a 14 percent lower relative risk within 90 days	Further trials are needed to compare statins, which also have anti-inflammatory and immunomodulatory properties, together	(Reitz et al. 2020)
Intestinal flora	Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug	The mechanism of metformin in the treatment of type 2 diabetes is unclear	Metformin acts as a glucose-lowering agent by controlling the type of gut flora	Intestinal microbiota is altered by taking metformin, resulting in more therapeutic effects and fewer adverse events	(Wu et al. 2017)

Table 1 (continued)

Field	Research	Issue	Outcome	Expectation	Reference
Kidney disease	The Long-term Effects of Metformin on Patients With Type 2 Diabetic Kidney Disease	Efficacy and safety of metformin in individuals with renal impairment in patients with type 2 diabetes	Patients with type 2 diabetes with renal insufficiency benefit from metformin without an increased risk of lactic acidosis	Further trials are needed to see if diabetic patients with moderate to severe kidney disease benefit from metformin	(Kwon et al. 2020)
Osteoporosis	Metformin use is associated with a lower risk of osteoporosis/vertebral fracture in Taiwanese patients with type 2 diabetes mellitus	Research on whether metformin reduces the risk of osteoporosis and vertebrae fractures is lacking	Metformin may reduce the risk of osteoporosis and/or vertebral fracture in patients with T2DM	As a potentially good osteoporosis prevention drug, whether metformin has a synergistic effect with other anti-osteoporosis drugs deserves further investigation	(Tseng 2021)

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Declarations

Conflict of interest The authors confirm that there are no conflicts of interest.

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