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REVIEW

The role of AMPK-dependent pathways in cellular and molecular mechanisms of metformin: a new perspective for treatment and prevention of diseases

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Abstract
Metformin can suppress gluconeogenesis and reduce blood sugar by activating adenosine monophosphate-activated protein kinase (AMPK) and inducing small heterodimer partner (SHP) expression in the liver cells. The main mechanism of metformin's action is related to its activation of the AMPK enzyme and regulation of the energy balance. AMPK is a heterothermic serine/threonine kinase made of a catalytic alpha subunit and two subunits of beta and a gamma regulator. This enzyme can measure the intracellular ratio of AMP/ATP. If this ratio is high, the amino acid threonine 172 available in its alpha chain would be activated by the phosphorylated liver kinase B1 (LKB1), leading to AMPK activation. Several studies have indicated that apart from its significant role in the reduction of blood glucose level, metformin activates the AMPK enzyme that in turn has various efficient impacts on the regulation of various processes, including controlling inflammatory conditions, altering the differentiation pathway of immune and non-immune cell pathways, and the amelioration of various cancers, liver diseases, inflammatory bowel disease (IBD), kidney diseases, neurological disorders, etc. Metformin's activation of AMPK enables it to control inflammatory conditions, improve oxidative status, regulate the differentiation pathways of various cells, change the pathological process in various diseases, and finally have positive therapeutic effects on them. Due to the activation of AMPK and its role in regulating several subcellular signalling pathways, metformin can be effective in altering the cells' proliferation and differentiation pathways and eventually in the prevention and treatment of certain diseases.

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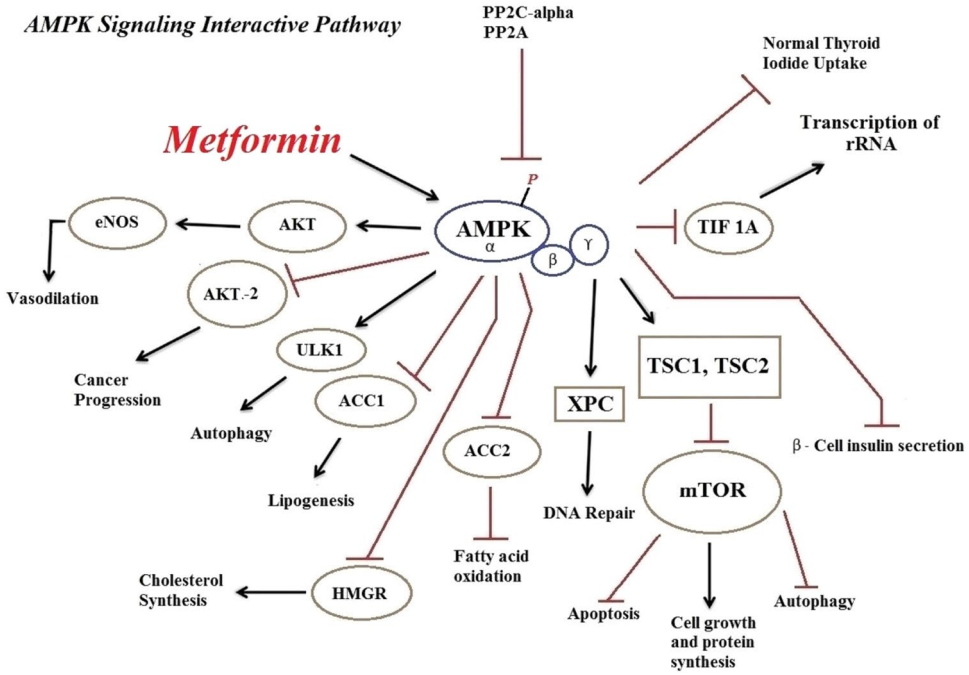
Graphical abstract



Keywords AMPK · Metformin · Diseases

Introduction

Metformin is known as one of the oldest, and most widely used oral medications in the treatment of type two diabetes or diabetes mellitus (Beladi Mousavi 2012; Taleb et al. 2014). As a result of metformin's activity, the mitochondrial respiratory chain complex (MRCC) (Baur and Birnbaum 2014) is blocked, the rate of glucose production from glycogen in liver cells is reduced, and sensitivity to insulin and glucose uptake through the activation of the adenosine monophosphate-activated protein kinase (AMPK) increases in the liver and peripheral tissues (Ismaiel et al. 2016; Mummidi et al. 2016; Wang et al. 2016). Metformin can suppress gluconeogenesis and reduce blood sugar by activating AMPK and inducing small heterodimer partner expression in the liver (Kim et al. 2008; Chanda et al. 2009). AMPK is a heterothermic serine/threonine kinase made of a catalytic alpha subunit and two subunits of beta and a gamma regulator (Oakhill et al. 2009; Hasanvand et al. 2016). This enzyme can measure the intracellular ratio of AMP/ATP. If this ratio is high, the amino acid threonine 172 available in its alpha chain would be activated by the phosphorylated liver kinase B1 (LKB1), leading to AMPK activation (Young and Zaha 2012; Hardie 2015). In other words, since it is an intracellular energy sensor, AMPK interferes with the regulation of glucose, cellular as well as whole-body energy homeostasis, and fatty acid metabolism (Shaw et al. 2005; Bright et al. 2009; Oakhill et al. 2009). Moreover, the muscle activity, physiological stress and oxidative factors are also able to activate the AMPK (Kim, Yang et al. 2016).

AMPK, metabolic and non-metabolic pathways

Several studies have examined the role of AMPK signalling pathway in various metabolic processes. This enzyme inhibits anabolic pathways (ATP consumer), and activates catabolic pathways to re-supply the cellular energy sources. The results of a study conducted by Suet Ching Chen in 2017 revealed that metformin can suppress adipogenesis through processes that are either dependent or independent of AMPK (Chen et al. 2017). Moreover, the effect of metformin independent of AMPK depends on the cell type and its evolutionary stage. Metformin in AMPK-mediated mechanisms leads to reduced liver glucose production and an increase in its consumption. AMPK is, indeed, considered as the main regulator of sugar and fat metabolisms. Ampk activation results in a diminish in the production of lipogenic enzymes, the induction of fatty acids oxidation, and a reduction in the activity of Acetyl-CoA carboxylase enzyme (Zhou et al. 2001; An and He 2016). Furthermore,

the chronic activation of AMPK will induce the expression of hexokinase and glucose carrier (Zhou et al. 2001). In a research conducted on experimental model, it was revealed that the intra-duodenum injection of metformin into these rats could reduce glucose production from liver cells via the activation of AMPK of duodenum mucosa (Duca et al. 2015). Moreover, several studies have confirmed the role of the AMPK pathway in the reduction of lipid mass of the body and improvement of NAFLD by inducing liver fatty acid oxidation (Zang et al. 2004a, b; Smith et al. 2016). It has recently been found that AMPK acts as an inhibitor of Farnesoid X receptor (FXR). FXR regulates lipid and glucose metabolism, and is involved in controlling the production and circulation of bile acids in the liver. The cultivation of liver and intestinal cells revealed that AMPK activity would inhibit FXR transcription (Brandmaier et al. 2015). It has been indicated in some studies that occurrence of intermediate fibrosis in the omental fat storage of obese people, which is associated with AMPK deactivation, results in TGF-β/SMAD3 signalling pathway induction, activation of myofibroblasts and apoptosis of adipocytes. Metformin is capable of preventing other complications and development of fibrosis via activating AMPK and suppressing the TGF-β/SMAD3 pathway (Luo et al. 2016).

AMPK is able to participate in various non-metabolic pathways, including nitric oxide synthesis and anti-inflammatory processes (Reihill et al. 2007; Salminen et al. 2011; Salt and Palmer 2012). Metformin is involved in controlling oxidative stress by controlling complex I of the mitochondrial electron transfer chain (Kinaan et al. 2015; Wiernsperger 2015) and can be effective in reducing kidney damage induced by gentamicin (Darabi and Hasanvand 2018; Hasanvand 2018). Many studies have shown that the anti-inflammatory and antioxidative stress effects of metformin in various diseases, such as rheumatoid arthritis, neuropathic pain, renal disorders and Ankylosing spondylitis (Son et al. 2014, Afshari et al. 2018, Driver et al. 2018, Qin et al. 2018a, b, Rajaei, Haybar et al. 2018). This effect of metformin is achieved via activating multiple signalling pathways, including AMPK and Pi3K/AKT. Accordingly, it can attenuated the levels of inflammatory cytokines, including TNF-α, Nrf2, IL-6 and etc. (Yan, Zhou et al. 2015, Ci, Zhou et al. 2017). Furthermore, metformin reduces the levels of inflammatory cytokines by inducing stimuli caused by lipopolysaccharide, activation of AMPK, and inhibition of phosphorylation of JNK1 in macrophages (Woo, Xu et al. 2014). AMPK chemical activators such as metformin reduce the transcription of the NF-β factor and MDR1 expression in MCF-7/adr cells (Kim et al. 2011). Continuous activity of AMPK signalling inhibits this factor and its consequent inflammation (Cacicedo et al. 2004; Yang et al. 2010). Using AMPK activators, Chunfen Mo et al. indicated in a research that this enzyme has a role in stimulating the expression of the Nrf2 transcription factor. This transcription activating factor is one of the factors that are effective in antioxidant responses (Mo et al. 2014). Nrf2 targets several genes, including NQO-1, HO-1 and glutathione S-transferase (GST), hence plays a role in regulating the antioxidant system (Tkachev et al. 2011).

Different factors can activate macrophages and cause inflammatory conditions in diabetic patients. One of the most important of these factors is the AGEs (Qin et al. 2012; Jin et al. 2015). These factors have a receptor of RAGE/NF-β on the surface of the macrophages. Various investigations have revealed that RAGE signalling plays a pivotal role in inflammation caused by the activation of macrophages by AGE (Salminen et al. 2011; Huang et al. 2015). By activating AMPK, metformin is able to reduce the expression of RAGE and suppress NF-βB activity, and accordingly, reduce the expression of macrophage inflammatory cytokines, such as IL-1β, IL-6 and TGF-β. Moreover, metformin increases the expression of IL-10 anti-inflammatory cytokines (Cai et al. 2015, Zhou et al. 2016). Various investigations suggest the relationship between the formation of AGE and development of neurological disorders and inflammatory responses in diabetic patients. Ming-Min Chung indicated that the cultivation of human neural stem cells in the presence of AGE decreases the survival of these cells and increases the production of inflammatory cytokines and oxidative enzymes. Treatment with metformin results in reducing the expression of inflammatory transcription factors, such as NF-κB and IKK, and also decreasing the production of AGE (Chung et al. 2017). By phosphorylating and stimulating AMPK, metformin can increase the rate of expression of telomerase reverse transcriptase (hTERT) enzyme and postpone the aging process of endothelial cells (Karnewar et al. 2018).

The results showed that metformin could reduce the activity of MRCC-1 and eventually reduce oxygen consumption (El-Mir et al. 2000). This inhibition of MRCC-1 by metformin affects the AMP/ATP ratio and the NAD + / NADH ratio, which prevents gluconeogenesis (Apostolova et al. 2020).

Regulation of transcription of hepatic gluconeogenesis induced by metformin has various mechanisms, such as inhibition of CREB-mediated transcription of gluconeogenic genes through breducing cyclic AMP accumulation (Miller et al. 2013; Johanns et al. 2016). In addition, activation of AMPK by metformin could reduce the expression of gluconeogenic gene. It has been suggested that decreased expression of G6pc and Pck1 may be due to separation of the CREB transcription set and mediated by AMPK activity (He et al. 2009).

AMPK and cellular differentiation

In a recent research conducted by Wei et al. the role of metformin in increasing the differentiation of dental pulp cells into odontoblast was examined. In this research, metformin could induce differentiation and mineralization of dental pulp cells and be effective in the reconstruction of palpation ulcers via regulating AMPK activity. Moreover, the inhibition of AMPK reduced the activity of alkaline phosphatase (Qin et al. 2018a, b). Metformin also significantly activated AMPK in bone marrow progenitor cells (BMPCs). Prescription of metformin in a time-dependent manner stimulates the differentiation of BMPCs into osteoblast by activating specific osteoblast transcription factors, such as Runx2/Cbfa1 and activating AMPK (Molinuevo et al. 2010). As the activation of AMPK was intensified by metformin, phosphorylation of the STAT3 transcription factor was reduced. This factor is central to the stimulation of conversion monocyte to macrophage by regulating the signalling of pro-inflammatory events and creating inflammatory micro-environment. Hence, as its phosphorylation is reduced by AMPK, this differentiation pathway is disrupted and inflammation will be more likely to be reduced (Vasamsetti et al. 2015). Moreover, the oral prescription of metformin in the systemic lupus erythematosus disease prevents the differentiation of *B* cells into antibody-producing plasma cells by inhibiting the mTOR/STAT3 signalling pathway (Lee et al. 2017). It has been found that metformin increases the proliferation of regulatory *T* cells and raises the expression of its specific transcription factor (FOXP3) by reducing the expression of STAT3 and increasing the expression of STAT5 (Passerini et al. 2008; Goodman et al. 2011; Maddur et al. 2012). This effect is simultaneously observed with reduced power of proliferation of TH17 cells. Metformin can alter the pathway of polarity of cell differentiation from the inflammatory phenotype of TH17 to the Treg inhibitory phenotype by regulating this pathway (Lee, Lee et al. 2015a, b).

Through its effect on multiple factors, the AMPK activity can alter the differentiation pathway of macrophages towards anti-inflammatory phenotype. In fact, if macrophages are stimulated by anti-inflammatory factors, AMPK phosphorylation occurs and the macrophage phenotype would be of anti-inflammatory type. Moreover, AMPK dephosphorylation occurs if macrophage is exposed to inflammatory cytokines (Sag et al. 2008). However, it was revealed, in tumor conditions, that metformin might be involved in inhibiting the spread of tumors and suppressing cancer development by altering the pathway of tumor-associated macrophages (TAMs) from phenotypes M2 to M1. Classic macrophages or M1 have pre-inflammatory activity and the alternative type or M2 has an inhibitory effect on immune responses, particularly on anti-tumor responses (Mukhtar et al. 2011; Ding et al. 2015). Chi-Fu Chiang et al. indicated that metformin-treated cancer cells increase the production of cytokines such as IL-12 and TNF-α, which act as macrophage inhibitors to the inflammatory phenotype or M1 by activating the signalling pathway of AMPK/NF-β. Moreover, the activation of this pathway reduces the production of inhibitory cytokines, such as IL-10, IL-4, IL-13 and TGF-β, and suppresses the differentiation of macrophages towards the anti-inflammatory phenotype M2. As a result of these processes, the microenvironment surrounding the cancer cells or the tumor is likely to suppress the tumor and destroy cancer cells (Chiang et al. 2017).

Activation of AMPK–mTOR via metformin inhibits the complex activity of the MRCC, which ultimately leads to cell death or inhibition of cell proliferation by growth factors (Cai et al. 2016). Akt kinase is an important kinase in human kinoma, which has three subtypes such as AKT1, AKT2, and AKT3. AKT2 subtype has been shown to play an important role in breast cancer and its proliferation and cell survival (Santi and Lee 2011). However, the increasing of expression of miR-200c and its effect on the activity pathway of AKT2, c-Myc and Bcl-2 thourth by metformin therapy and its antitumor effects may indicate the anti-cancer potency of metformin and AMPK (Pulito et al. 2014; Zhang et al. 2017).

Metformin and therapeutic goals

Therapeutic actions of metformin in COVID-19

With the advent of coronavirus in 2019, many studies have been conducted with regard to its treatment. However, the ACE2 receptor has been shown to facilitate infection at the surface of coronary target cells (Guan et al. 2020, Hoffmann et al. 2020). It has been indicated that metformin activates the AMPK pathway that can ultimately prevent the virus binding to the receptor by phosphorylating the ACE2 receptor and altering its structure (Sharma, Ray et al. 2020). Studies have shown that two proteins in humans that are regulated by the mTOR signalling pathway interact with coronavirus proteins (Sharma, Ray et al. 2020). Moreover, it has been indicated that the AMPK signalling pathway can inhibit the mTOR pathway (Ramaiah 2020). Meanwhile, functional disorders of vital organs of the body, which are among the most important coronary complications, including endothelia, cardiovascular, hematological, and brain disorders, etc., are affected by oxidative stress and inflammation processes. Activation of the AMPK pathway and subsequently inhibition of mTOR, suppression of oxidative stress and inflammation, and inhibition of the increase in genes encoding

proinflammatory cytokines, enables metformin to reduce mortality in patients with confirmed COVID-19 (Kamyshnyi et al. 2021). Decreased endosome cell pH has been shown to be associated with increased maturation of coronary virion, and metformin inhibits the endocytic cycle and maturation of virions by increasing the pH level. On the other hand, it can be effective in reducing the mortality of these patients by preventing the disruption of the normal intestinal flora, (Varghese, Samuel et al. 2021). Studies have shown that metformin can have a reduced risk of death in COVID-19 patients. This effect was mediated by inhibits mTORC1 and active LKB1 by AMPK phosphorylation (Kamyshnyi et al. 2021). Recent studies have shown that the use of metformin by AMPK activation can phosphorylate ACE2 and increase the stability of ACE2 and then decrease the host cell acceptance level for SARS-Cov-2 (Bangi et al. 2020, Sharma, Ray et al. 2020, Shen et al. 2020). Induction of the AMPK signalling pathway by metformin effectively reduces and modifies neutrophil extracellular trap activity and suppresses the inflammatory response in SARS-CoV-2 (Sharma, Chang et al. 2020, Kamyshnyi et al. 2021). In addition, Esam Z. et al. Also showed that the use of metformin could reduce the risk of lung fibrosis associated with SARS-Cov-2 (Esam 2020). There are numerous other studies in this area, all of which suggest that metformin may be a useful adjunctive therapy for COVID-19 patients (Bhutta et al. 2021, Bielka et al. 2021, Ibrahim et al. 2021, Varghese, Samuel et al. 2021, Zangiabadian et al. 2021).

Therapeutic actions of metformin as an anti-cancer agent

The relationship between the spread of tumors and cell metabolism processes, particularly the role of AMPK in these processes, has been investigated in various researches over a long period of time, and their use in developing new anti-cancer strategies are being examined (Cairns et al. 2011). The mTOR signalling pathway has a significant role in controlling the translation and construction of protein, spread of lymphocyte population, tumor genesis and drug resistance (Weichhart and Saemann 2009; Witzig and Gupta 2010; Perez-Galan et al. 2011; Zoncu et al. 2011). Epidemiological investigations have shown that using metformin is associated with reduced incidence of various types of cancers including pancreatic (Li et al. 2009), colon (Currie et al. 2009), breast (Bodmer et al. 2010), and prostate cancers (Wright and Stanford 2009). The results of different investigations have emphasized that metformin is highly likely to inhibit mTOR and perform its anti-tumor role by activating AMPK. Moreover, the AMPK Alpha subunit interacts with mitotic and cytokine regulators. This process is also associated with the suppressing role of AMPK in combating various kinds of cancers (Vazquez-Martin et al. 2009a, b; Green et al. 2010).

Moreover, another study conducted by Tao Lu et al. stated that exposure to metformin thourth regulating AMPK–CEBPB–PDL1 signalling pathway can a significant reduction in the risk of non-small cell lung cancer (Lu et al. 2021). Also, Zhuang Luo et al. showed that metformin can induces apoptotic cytotoxicity and finally degradation thourth AMPK/PKA/GSK-3β-mediated in non-small cell lung cancer (Luo et al. 2019). Various research have shown that the combination therapy of metformin with anticancer drugs mades synergic anticancer effects, such as radiation (Storozhuk et al. 2013), gefitinib (Morgillo et al. 2013; Li et al. 2017), erlotinib (Wang et al. 2017), sorafenib (Groenendijk et al. 2015), car-boplatin (Liu et al. 2017), cisplatin (Lin et al. 2013), and TRAIL (Nazim et al. 2016).

Park et al. reported that metformin regulates β-catenin to reduce cell proliferation by activating AMPK in colon carcinoma (Park et al. 2019) and other study showed that in colorectal cancer cells, inhibits non-canonical Ser552 phosphorylation in β-catenin through an AMPK/PI3K/Akt activation with metformin (Amable et al. 2019). The role of AMPK and its downstream pathway in repression of protein prenylation through MVA pathway and LKB1/AMPK pathway is linked to inhibition of tumor growth has also been reported in several study (Carretero et al. 2007; Seo et al. 2020). In another study demonstrated that activating ampk by metformin attenuated tight junction assembly in intestinal epithelium and promotes expression of colonic epithelial Caco2 cells (Chen, Wang et al. 2018). Several studies have shown that activation of cells (Vazquez-Martin et al. 2009a, b; Yi et al. 2017). Metformin inhibits the progress of cells in cancer by inducing AMPK and then LKB1 levels and ultimately inhibits translation. Also, metformin reduces the phosphorylation of S6Ks and prevents mTOR activity (Saraei et al. 2019). Metformin effectively decrease the risk of proliferation and metastasis of pancreatic cancer (Oliveria et al. 2008; Ruiter et al. 2012). In addition, evidence suggests that a reduced risk of pancreatic cancer suggests that significant inhibition of mTOR may be TSC2-independent or dependent but associated with phosphorylated AMPK (Dowling et al. 2007; Gwinn et al. 2008; Mohammed et al. 2013).

Therapeutic actions of metformin as a nephroprotective agent

It has also been indicated that metformin can have a nephroprotective effect by activating the AMPK signalling pathway (Hasanvand et al. 2018). Another research revealed that AMPK activation by metformin was associated with reduced TGF-β-induced collagen production in kidney fibroblasts in mice. This factor, which is considered as one of the

important fibrogenic cytokines, plays a significant role in the pathogenesis of kidney diseases (Hills and Squires 2011; Lu et al. 2015; Hasanvand and Saberi 2018). Moreover, the positive effect of metformin in reducing the incidence of nephropathies in diabetic patients has been confirmed (Rafieian-Kopaei 2013; Dissanayake et al. 2017). This drug prevents the formation of kidney stones with its antioxidant activity (Yang et al. 2016). It has been shown that treatment with metformin, as an AMPK agonist, can well moderate mitophagia in epithelial cells of the proximal tubule of the kidney (Zhao and Sun 2020). In addition, Ya-chun Han et al. Also showed that the use of metformin could decrease the risk of fibrosis in the renal interstitial tube associated with mitophage activation via the AMPK-Pink1-Parkin pathway (Han et al. 2021). Another study showed that the use of metformin in renal nephrectomy models following renal disease could halt the progression of chronic renal disease, including renal fibrosis, and that activation of AMPK may contribute to the protective effect of metformin nephroprotechnics (Borges et al. 2020). Based on several clinical trials, metformin has shown beneficial therapeutic effects on the survival of CKD patients as well as the survival of a transplanted kidney (Stephen et al. 2014; De Broe et al. 2018).

Therapeutic actions of metformin as a neuroprotective agent

A study has shown that stimulation of AMPK is a major molecular mechanism of "feeding behaviour" in the hypothalamus of the brain (Blanco Martinez de Morentin, Gonzalez et al. 2011). In vitro studies have shown that stimulation of AMPK reverses neuropathic allodynia. Moreover, metformin could diminish chemotherapy-induced neuropathic pain in animals (Taylor et al. 2013). In rat models, metformin has been shown to have antinociceptive effects on the alleviation of pain in nerves damaged by diabetes (Ma et al. 2015). Metformin administration could up-regulate the expression of intrinsic factors linked to nerve regeneration such as apolipoprotein E (ApoE) after nerve damage (Melemedjian et al. 2013). It was indicated in animal models of focal cerebral ischemia studies conducted by Harada et al. that neuroprotective effects of AMPK signalling activated by metformin diminishes the glucose intolerance. Moreover, they have reported a decrease in variation in the mnemonic tests (Harada et al. 2010). Activation of AMPK could be considered as a novel therapeutic purpose for the tentative treatment of neuropathic pain (Yerra et al. 2018). It was reported that activation of TRPA1 could induce pain-related behaviors in mice (Miura et al. 2013). However, treatment with AMPK activators could attenuate these behavioral and molecular changes in the pathophysiological profile of metabolic dysfunction (Wang et al. 2018). Various studies have shown that treatment with metformin is effective in neurological diseases, including high MPTP and increased BDNF (Patil et al. 2014, Lu et al. 2016), Parkinson's disease (Choi et al. 2010; Arbeláez-Quintero and Palacios 2017; Lu et al. 2020, Paudel et al. 2020), epilepsy (H S, Paudel et al. 2019, Demaré et al. 2021; Sanz et al. 2021, Salvati et al. 2022), traumatic brain injury (Tao et al. 2018; Taheri et al. 2019; Fan et al. 2020; Rahimi et al. 2020), neuroprotection of the heart (Zhu et al. 2018, Benjanuwattra et al. 2020, Leech et al. 2020), and preconditioning in ischemic brain injury (Wang et al. 2021a, b, c). Various studies have shown that BDNF can affect the structure of the anal sphincter (Singh and Rattan 2021, Singh, Singh et al. 2021).

Therapeutic actions of metformin as a cardioprotective agent

Consumption of metformin in diabetic patients is associated with a significant reduction in cardiac infarction and atherosclerosis (Matsumoto et al. 2004). With its effect on reducing the recruitment of monocytes to the vascular wall and their differentiation into inflammatory macrophages, metformin reduces the formation of atherosclerotic plaques and decreases the levels of inflammatory cytokines (Vasamsetti et al. 2015). The effects of metformin are mediated through an increase in p-AMPK and by up-regulating p-eNOS. Moreover, it improves cardiac function. The cardioprotective effects of metformin are independent of its antihyperglycemic effects. Moreover, an improved myocardial remodelling after an ischemic insult with metformin use was indicated in a research (Varjabedian et al. 2018). A study in patients showed that the progression of the medial thickness of the carotid artery was reduced in metformin-treated diabetic patients. The median thickness of the carotid artery is a known indicator of atherosclerotic progression. It has also been indicated that activation of AMPK by metformin can have a pleiotropic effect (Zang et al. 2004a, b; Vasamsetti et al. 2015). Additionally, various studies have shown that treatment with metformin is effective in heart diseases, including cardiotoxicity (Kuburas et al. 2022, O'Neill et al. 2022, Park, Park et al. 2022), heart failure (Benes et al. 2022, Buczyńska et al. 2022, Hendawy et al. 2022), atrial fibrillation (Bai et al. 2019; Liu et al. 2020, Zhou et al. 2022), coronary heart disease (Hua et al. 2018; Luo et al. 2020).

Therapeutic actions of metformin in reproductive system diseases

In a research conducted by HyeRan Gwak et al. in 2017, the mechanism of action of metformin on ovarian cancer was examined. The results of this research confirmed that metformin can inhibit AKt and P70S6K by activating AMPK. Following this process, the GSK3β protein is activated, and finally during the ubiquitin/ proteasome process, the value

of cyclin D1 decreases. In fact, metformin decreases the amount of cyclin D1 without affecting its transcription levels (Gwak et al. 2017). Cyclin D1 is an essential regulator of the cell cycle in phase G1. Investigations have indicated that high expression of this factor is associated with resistance to treatment and prognosis of ovarian cancer (Bali et al. 2004; Hashimoto et al. 2011). Activation of AMPK by metformin in ovarian syndrome or metabolic syndrome in vitro and in vivo results in the inhibition of metabolism, cessation of the cell cycle, and finally apoptosis of cells (Ben Sahra et al. 2008; Pierotti et al. 2013). Research studies have shown that using metformin is associated with improved semen parameters and testicular weight, reduced apoptosis in testicular cell, and finally restoration of hormonal homeostasis (Yan, Mu et al. 2015a, b). Indeed, metformin administration in STZ-diabetic rats resulted in improved testosterone, LH and FSH hormones levels (Nasrolahi et al. 2013). Various studies have shown that treatment with metformin is effective in reproductive system diseases, including female and male reproduction in endocrine pathologies (Lee et al. 2019; Shpakov 2021, ul haq Shah, Shrivastava et al. 2022), endometriosis (Zhao et al. 2018, Mu et al. 2020, Stochino-Loi et al. 2021, Kimber-Trojnar et al. 2022), polycystic ovary syndrome (Chen et al. 2019; Fornes et al. 2022, Xu et al. 2022) and prostate (Sun et al. 2018, Chen, Wang et al. 2021a, b, c, Aydın et al. 2022, Morale et al. 2022).

Therapeutic actions of metformin in the bone structure

Available evidence suggests the occurrence of fibroblasts asphyxiation and blockage of AMPK activity in the ankylosing spondylitis disease. Moreover, laboratory investigations conducted on metformin have indicated its anti-osteogenic effects and also its agonist property concerning AMPK. Findings of the research carried out by Xiong Qin et al. in 2018 showed that osteogenic markers and inhibition of ossification are reduced significantly by metformin prescription to fibroblasts extracted from patients with ankylosing spondylitis (Qin et al. 2018a, b). Metformin is able to suppress the differentiation of osteoblasts and inhibit the signalling pathway of OPG/RANKL/RANK (Shao et al. 2014). In another study carried out in 2010, the mechanism of metformin's activity on the differentiation of osteoblasts was examined. This research revealed that metformin could increase the expression of osteogenic genes such as bone sialoprotein, alkaline phosphatase, Runx2, osteocalcin, and SHP. Metformin induces the physical interaction and the formation of a complex between SHP and Runx2 in the osteocalcin promoter. The research findings showed that metformin might stimulate osteoblasts differentiation via changing the activation of Runx2 by upstream stimulatory factor-1 AMPK/USF-1/SHP (Jang et al. 2011). Min-Ji Ahn and Goang-Won Cho indicated, in a research conducted in 2017, that activation of AMPK by metformin could have a stimulatory role in human bone marrow mesenchymal stem cells towards neural differentiation (Ahn and Cho 2017). Various studies have shown that treatment with metformin is effective in bone structure, including osteoarthritis (Feng et al. 2020; Li et al. 2020a, b; Li et al. 2020a, b), osteoporosis (Blümel et al. 2020, Guo et al. 2022, Song et al. 2022), bone regeneration (Ren et al. 2021; Fang et al. 2022; Sun et al. 2022) and osteosarcoma (Paiva-Oliveira et al. 2018; Zhao et al. 2019, Lu et al. 2021).

Therapeutic actions of metformin in digestive system diseases

Min-Jie Lin et al. showed that activation of the metformin / AMPK pathway could improve the non-alcoholic fatty liver disease in obese mice (Lin et al. 2017a, b). Stimulation of this pathway has a positive effect on the activity of the LXRα transcription factor. This factor results in the decreasing regulation of expression of apolipoprotein (Jakel et al. 2004; Shu et al. 2007; Shu et al. 2010; Gao et al. 2012). Hence, due to the influence on the reduction of its expression in the aforementioned process, metformin ameliorates this complication (Lin et al. 2017a, b). Another study revealed that metformin could play an inhibitory role in the cell proliferation of Esophageal squamous cell carcinomas by positive regulation of AMPK, P53, P21 and P27 (Cai et al. 2015). Metformin significantly reduces the severity of inflammatory bowel disease (IBD) via suppressing the signalling pathway of STAT3. As the expression of STAT3 transcription factor is increased in this disease, the TH17 phenotype and the production of inflammatory cytokines, particularly IL-17, IL-6 and TNF-α increase. Metformin can reduce the expression of STAT3 and increase the expression of P53 through the AMPK pathway, which is in the upstream of the mTOR transcription factor. Regulation of these conditions improves the clinical status of IBD patients by reducing inflammation (Shackelford and Shaw 2009, Micic et al. 2011, Gálvez 2014, Lee, Lee et al. 2015a, b). Furthermore, another investigation revealed that inhibiting the activation of the two pathways of STAT3 and NF-βB by AMPK has been effective in inhibiting the growth of pancreatic tumours (Tan et al. 2015). In addition, various studies have shown that treatment with metformin is effective in digestive system diseases, including colitis (El-Mahdy et al. 2021, Liu, Liao et al. 2021, El-Ghannam et al. 2022), Pancreatitis (He et al. 2021, Wang et al. 2021a, b, c, Wang, Yu et al. 2021), Liver Disease (Saeedi Saravi et al. 2016, Pinyopornpanish et al. 2021, Xie, Wang et al. 2021a, b, c) and Gut Microbiota (Lee, Chae et al. 2021b, a, Lee, Kim et al. 2021, Liu, Liao et al. 2021).

Conclusions

Many studies have investigated the role of metformin in the treatment of various diseases, including inflammatory diseases, autoimmune diseases and cancer. A considerable number of these investigations have revealed that the capacity of metformin to activate AMPK and also the consequent activation or inhibition of different factors by metformin enable it to alter the pathological pathways of the disease, direct cell differentiation, and moderate the inflammatory conditions. Since its therapeutic use, even at high doses, does not lead to severe side effects, metformin has a significant role in either treating various diseases or reducing their symptoms.

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Data availability Enquiries about data availability should be directed to the authors.

Declarations

Conflict of interest The author have not disclosed any conflict of interest.

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