Chapter

Metformin: Pros and Cons

Shalini Sivadasan, Muthukumar Subramanian and Rajasekaran Aiyalu

Abstract

Metformin was approved for the treatment of Type 2 Diabetes Mellitus in 1958 for UK, in 1972 for Canada and in 1995 by FDA in USA. Metformin is the drug of choice for patients who are obese and have type 2 diabetes mellitus. Though metformin was at first proven to treat hyperglycemia, many other uses of metformin are proven to be effective. It is also used for gestational diabetes mellitus, obesity, hyper secretion of ovarian androgen, poly-cystic ovary syndrome (PCOS), anti-psychotic therapy induced weight gain, cancer treatment and anti-aging. Metformin causes a decrease in appetite thus known to act on obesity. The other action of metformin is reduction of circulating levels of insulin and insulin like growth factor 1 (IGF-1) which is associated with anticancer action. There are ongoing researches about the effect of metformin on anti-aging properties and proved that metformin is linked with anti-aging factors. Three main factors that are related with aging are oxidation, glaciation and methylation. Metformin as all drugs, have unwanted effects as well. Many side effects of metformin are considered mild where lactic acidosis and vitamin B12 deficiency happens to be the major.

Keywords: metformin uses, diabetes mellitus, obesity, poly-cystic ovary syndrome, cancer

1. Introduction

1.1 Pros (uses) of metformin

Metformin, the most common drug used to treat type 2 diabetes, approved by U.S. Food Drug Administration (US-FDA) (1), belongs to a class of drugs called biguanides with a guanidine and galegine connection. Metformin was approved for treatment of Type 2 Diabetes Mellitus in 1958 for UK [1], 1972 for Canada [2] and 1995 by FDA in USA [1, 3].

Metformin (1,1-dimethyl biguanide hydrochloride) was synthesized in 1920's. Since then, the drug became the first choice to treat type 2 diabetes due to its remarkable ability to decrease plasma glucose levels [4–6]. It acts by reducing the glucose made by liver, decreasing the amount glucose that body absorbs and increasing the effect of insulin in the body [7].

In recent years, studies have shown many unexpected effective roles of metformin that exerts strong effect on cardiovascular disease (CVD) [8], cancers [9, 10], neurodegenerative diseases [11], liver diseases [12], obesity [13, 14], and renal diseases [15], hypersecretion of ovarian androgens, poly-cystic ovary syndrome (PCOS), anti-psychotic therapy induced weight gain, and anti-aging [16].

The agent also offers neuro protection that may reduce the risk of dementia and stroke [17].

1.1.1 Metformin in diabetes

Several studies and clinical trials have confirmed that metformin mono therapy or combination therapy with other glucose-lowering drugs is successful in treating type 2 diabetes. Metformin is the drug of choice for diabetic patients who are obese and have type 2 diabetes mellitus.

Type 2 diabetes coexists with insulin resistance and leads to extremely high blood sugar levels. Metformin lowers blood sugar, preventing permanent organ damage, which in due course could lead to dysfunction and failure [18, 19]. Metformin exerts its anti-hyperglycemic effects through AMP which initiates the uptake of sugar from the blood into muscles.

Metformin exerts its anti-hyperglycemic effects by suppressing hepatic glucose production through AMPK dependent [20, 21] or -independent pathways [22, 23].

Metformin increases AMPK that leads to more sugar being taken from the blood into tissues, thus lowering the blood sugar level [24].

It is used in case of insulin resistance as it works by decreasing hepatic glucose production, decreasing peripheral insulin resistance and improving insulin sensitivity thereby increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycaemia and does not cause hyperinsulinemia in normal patients or in patients with type 2 diabetes. Insulin secretion remains unchanged whereas fasting insulin levels and daylong plasma insulin response may decrease with metformin therapy [25].

On the other hand, metformin may reduce blood sugar by inhibiting the production of new glucose (gluconeogenesis) from non-carbohydrates such as lactate, glycerol, and some amino acids [23]. Metformin inhibits gluconeogenesis through AMPK-dependent activation of small hetero dimer partner (SHP) and inhibition of phosphorylation of CREB binding protein (CBP) [26], thereby suppressing the expression of gluconeogenic genes, such as G6Pase (glucose 6 phosphatase), PEPCK (phosphoenolpyruvate carboxykinase), and PC (pyruvate carboxylase) [27].

Studies also suggest that metformin could enhance GLUT1 (glucose transporter 1) mediated glucose transport into hepatocytes by activating IRS2 (insulin receptor substrate two), decreasing plasma glucose levels [28].

Besides decreasing liver glucose production, metformin also decreases glucose levels through increasing (i) GLUT4 (glucose transporter 4) mediated glucose uptake in skeletal muscles [29] and (ii) absorption of glucose in the intestines [30]. Metformin also stimulates glucagon-like-peptide-1 (GLP-1) release, thereby improving insulin secretion and reducing plasma glucose levels [31]. The molecular mechanism of metformin in hepatic gluconeogenesis and glucose production is shown in **Figure 1**.

A clinical trial conducted on over 3,000 people who were at risk of developing type 2 diabetes showed that those people treated with metformin had a 31% lower occurrence of type 2 diabetes compared to the placebo group [34].

1.1.2 Metformin in gestational diabetes

Gestational diabetes mellitus (GDM) is the most common medical complication of pregnancy which is associated with insulin resistance (IR) and hyperinsulinemia that may predispose some women to develop diabetes. Gestational diabetes has been defined as any degree of glucose intolerance with an onset, or first recognition during pregnancy [35]. In 2013, the World Health Organization (WHO) recommended

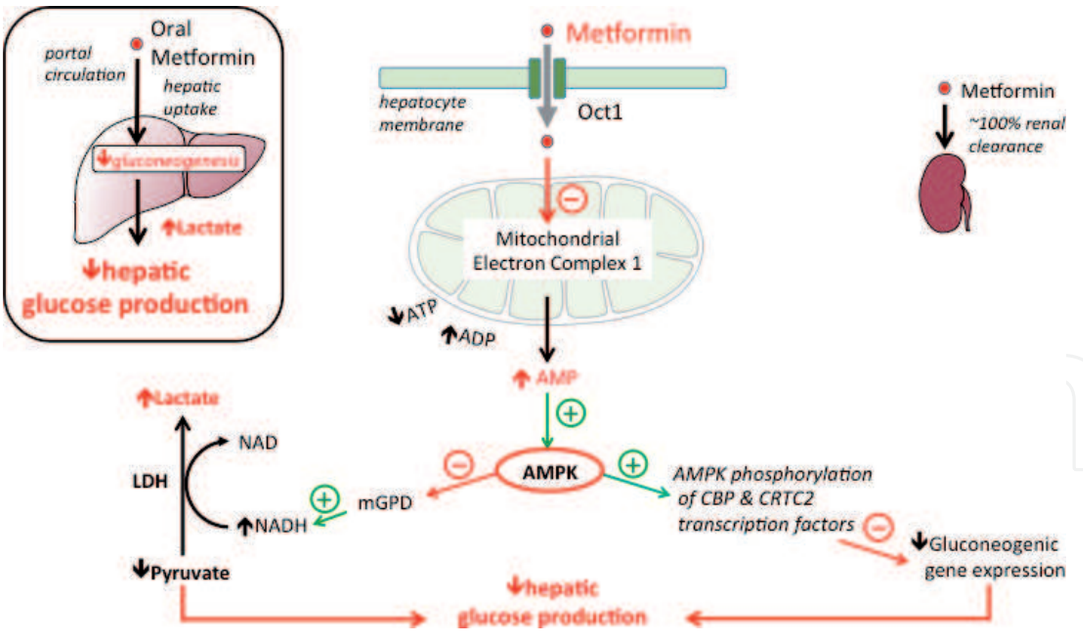

Figure 1.
Metformin in hepatic gluconeogenesis and glucose production. Metformin acts primarily to suppress glucose production in the liver. While metformin's mechanism(s) of action remain controversial, current evidence indicates that metformin's most important effect in treating diabetes is to lower the hepatic production of glucose [32, 33].

that hyperglycemia first detected during pregnancy be classified as either 'diabetes mellitus (DM) in pregnancy' or 'GDM' [36]. GDM is associated with short- and long-term sequelae on both, mother and offspring [37, 38].

During normal pregnancy, around the mid-pregnancy, a progressive insulin resistance develops that progresses during the third trimester. In early pregnancy, insulin secretion increases, while insulin sensitivity remain unchanged, decreased or increased whereas in mid pregnancy, insulin sensitivity declines progressively and worsens during the rest of the pregnancy, being worst in the late third trimester, which rebounds with the delivery of the placenta. Therefore, GDM usually develops in the late second trimester and disappears, instantly, post-delivery [39].

For GDM, lifestyle interventions such as daily exercise, medical nutrition therapy is the initial treatment while, metformin, the oral hypoglycemic agent is being considered as a substitute to insulin. The rationale behind using metformin in gestational and pre-existing diabetes during pregnancy is as metformin increases insulin sensitivity, reduces hepatic glucogeneogenesis and enhances peripheral glucose uptake, resulting in lowering of blood glucose with minimal risk of maternal hypoglycemia and weight gain [40].

Although, metformin has been shown to pass freely across the placenta [41], there are no reported adverse side effects to the fetus when it is used to treat women with infertility caused by poly-cystic ovary syndrome (PCOS) [42, 43]. Metformin is classified as a category B drug, which implies that there is no confirmation of animal or fetal toxicity or teratogenicity. The study of metformin in pregnancy revealed that the use of metformin in women with GDM was not associated with increased risk of congenital anomalies, or maternal and neonatal complications compared to insulin, except for higher rates of preterm labour [44].

Results of systematic review and meta-analysis had shown that metformin is better than insulin in reducing, maternal weight gain during pregnancy and the frequency of pregnancy induced hypertension, with no changes in the frequency of hypoglycemia and pre-eclampsia [45]. In addition, randomized controlled trials (RCT) suggest that metformin could be used to treat or

prevent pre-eclampsia [46]. Metformin is considered as the first-line drug in the management of type 2 diabetes due to its efficacy, tolerability and safety in non-pregnant individuals.

1.1.3 Metformin in polycystic ovary syndrome

Poly-cystic ovarian syndrome (PCOS) is a hormonal disorder often aggravated by obesity and insulin resistance. PCOS is an endocrine-metabolic dysfunction among 5–10% of women in reproductive age which is associated with metabolic disturbances that have a high impact in cardio metabolic diseases, such as insulin resistance [47–49].

PCOS is characterized by menstrual irregularities, low fertility, obesity and high blood levels of male hormones in reproductive aged women [50]. PCOS confirms insulin resistance which leads to the hypothesis of a pre-diabetic state with glucose intolerance, gestational diabetes mellitus and evident diabetes. Several studies show that insulin resistance stimulates the ovaries to produce male hormones, i.e., androgens. This causes stigmata of androgen excess such as hirsutism and acne. Metformin increases insulin sensitivity and decreases the production of ovarian androgen thereby normalizing the hormone levels, stabilizes menstrual irregularities and improves fertility and ovulation. It also directly inhibits the androgen production [51].

Metformin treats PCOS symptoms, such as irregular ovulation or menstrual cycles, and the excess of insulin in the body. It has also been made known to treat PCOS symptoms by reducing body mass index (BMI) and testosterone levels. Furthermore, metformin assists fertility and increases the chance of successful pregnancy and reduces the risk of early miscarriage, gestational diabetes, and inflammation associated with PCOS. Metformin is thus used as the drug of choice for the treatment of PCOS. More to that, metformin helps mothers carry their baby to full term [51, 52]. Metformin is strongly recommended in patients with metabolic syndrome and obesity [51].

1.1.4 Metformin in obesity

Obesity is a chronic disease accompanied with metabolic syndromes, such as diabetes, fatty liver diseases, and cardiovascular diseases (CVDs). Obesity is caused by an imbalance between energy intake and expenditure [53].

Metformin happens to be one of the drugs available for the treatment of obesity. Metformin acts on obesity by decreasing the appetite and reduced BMI levels. Metformin contains a primary anorectic factor which reduces the appetite. Leptin levels were found to be decreased on taking metformin. Moreover, glucagon like peptide-1 levels rise significantly on taking metformin. This promotes weight loss. It was observed that adults with severe obesity lost weight more significantly than mildly obese patients [54]. Metformin exerts its anti-obesity effects through increasing mitochondrial biogenesis, decreasing fatty acid uptake, and stimulating thermogenesis [55].

It acts by promoting sugar dysplasia restrains and reducing inhibition caused by insulin-induced expression of the glucose transporter protein, thus increasing glucose utilization [56]. Metformin is effective in reducing body weight and improving insulin sensitivity in adults, and is used to treat adolescents who are overweight or obese and unresponsive to changes in lifestyle or who present with insulin resistance [57]. Many studies support that metformin can promote weight loss in overweight or obesity patients [58, 59]. Based on the reports it is understood that clinical trials supports the efficacy and safety profiles of metformin in diabetes and weight gain prevention [60].

1.1.5 Metformin in medication induced weight gain

Studies have shown that use of antipsychotics increase the risk of weight gain, dyslipidemia and diabetes. Weight gain and abdominal adiposity which is directly associated with insulin resistance, dyslipidemia and risk of diabetes may be induced by second generation antipsychotics [61, 62]. Stimulation of appetite, reducing physical activity and impairing metabolic regulation is the mechanism of antipsychotics induced weight gain [63].

Metformin aids in weight loss. Drug induced weight gain can be reduced by metformin. It assists in reduction of weight for those who gain 10% of body weight than pre-treatment [63]. Metformin contains an anorectic factor and facilitates less hunger. This also aids in decreased appetite. Metformin causes decreased leptin levels, thus suppresses appetite. Metformin also increases the GLP-1 levels which enhances weight loss. Thus, metformin with lifestyle changes is effective in the treatment of weight gain induced by antipsychotics.

1.1.6 Metformin in cancer

New studies have shown that metformin is effective in killing cancer cells. In trials, people undergoing chemotherapy alone saw their cancer return, while for those on chemo and metformin, their tumors disappeared. Research has shown that those taking metformin are less likely to develop certain cancers. Metformin has been found to improve cancer prognosis as it inhibits cancer cell growth and proliferation. Evidence points that metformin inhibits growth, survival, and metastasis of different types of tumor cells, including those from breast, liver, bone, pancreas, endometrial, colorectal, kidney, and lung cancers [64].

Metformin prevented the growth and spreading of certain cancers in patients with type 2 diabetes. This proposed mechanism is through a known tumor-suppressant gene (LKB1), which activates AMPK. Metformin shows anticancer properties by direct and indirect regulation of cells' metabolism. The direct effects are mediated by AMPK dependent and -independent pathways. (i) Metformin activates AMPK, which leads to the inhibition of mTOR signaling, and thereby disturbs the protein synthesis, and suppresses the cell growth and proliferation [65]. As an antidiabetic drug, metformin decreases plasma glucose levels, thereby inhibiting cancer cell proliferation and survival [66].

Other studies reported that metformin could activate the immune response against cancer cells [67] or decrease NF-kB (nuclear factor-kB) activity, which results in a reduction in the secretion of pro-inflammatory cytokines [68].

Metformin activates AMPK and then induces p53 phosphorylation to prevent cell invasion and metastasis [69].

The different mechanisms antitumor action has been proposed which involves the following: (a) the activation of adenosine monophosphate kinase, (b) modulation of adenosine A1 receptor (ADORA), (c) reduction in insulin/insulin growth factors, and (d) inhibition of endogenous reactive oxygen species (ROS); and its resultant damage to deoxyribonucleic acid (DNA) molecule is another paramount antitumor mechanism [70].

Metformin reduces the proliferation of cancer cells and the possibility of malignancies in different types of cancer, including gastric carcinoma, pancreatic cancer, uterine cancer, medullary thyroid cancer [71]. **Figure 2** shows the mechanism of metformin in Cancer and **Figure 3** shows the direct and indirect effects of metformin in Cancer.

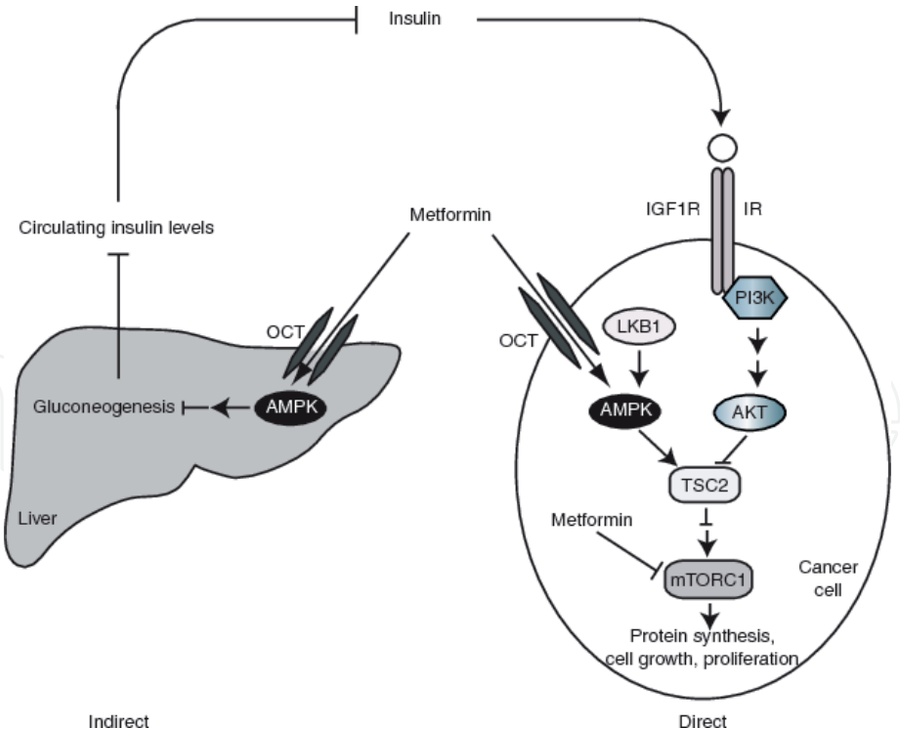

Figure 2.
Mechanism of metformin in Cancer. The anticancer activity of metformin is associated with direct and indirect effects of the drug. The direct insulin-independent effects of metformin are mediated by activation of AMPK and a reduction in mTOR signaling and protein synthesis in cancer cells [72].

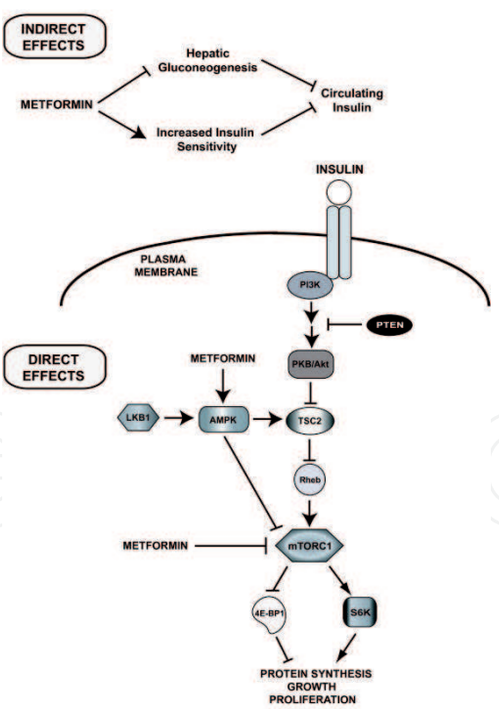

Figure 3.
Direct and indirect effects of metformin on cancer. Metformin activates AMPK leading to stabilization of TSC2 and inhibition of mTORC1 signaling and protein synthesis. Metformin can also directly target mTOR independently of AMPK and TSC2 [73].

1.1.6.1 Breast cancer

Breast cancer (BC) is one of the most common malignancies occurring in females. Cellular glucose metabolism is linked tightly with the proliferation and development of breast cancer. Several studies suggested that metformin reduces

the incidence of breast cancer in type 2 diabetes patients [74]. Cancer cells show enhanced glucose uptake and metabolism and prefer glycolysis. The noted specialty of metformin is to decrease glucose levels, thereby limiting the availability of energy for cancer cells. Metformin decreases FAS expression which is an essential component of the fatty acid synthesis pathway, therefore affecting the survival of cancer cells.

1.1.6.2 Blood cancer

Leukemia comprises 2.8% of all cancers and 3.4% of cancer-related deaths worldwide. The aberrant activation of the PI3K/AKT/mTOR pathway is one of the most common biochemical features of leukemia [75]. Metformin inhibits AKT/mTOR signaling, which is an effective approach to treat leukemia. Metformin plays a beneficial role in human lymphoma by inhibiting mTOR signaling without the involvement of AKT, and the suppression of mTOR subsequently leads to the suppression of growth of B cells and T cells [76].

1.1.6.3 Colorectal cancer (CRC)

CRC is also one of the most common cancers in the world. In 2004, relationship between metformin and CRC was demonstrated [77]. Metformin may exert its pharmacodynamic effects through the gut-brain-liver axis, but these mechanisms require further exploration. In the intestine, metformin increases glucose uptake and lactate concentrations. Administration of metformin increases the bile acid pool in the intestine that may affect GLP-1 secretion and cholesterol levels. In addition, metformin changes the microbiome, affecting the regulation of metabolism, such as glucose homeostasis, lipid metabolism, and energy metabolism [78]. These changes inhibits the development and progress of CRC.

1.1.6.4 Bone cancers

Compared with cancers initiating in bone tissue itself, invasion of metastatic cancers, especially breast, lung, and prostate cancers, into bones is more common [79]. All types of bone cancers influence the osteolytic process, and osteoblastic metastases occur through osteoclast activation or stimulant factors which are responsible for osteoblastic proliferation, differentiation, and formation [80].

1.1.6.5 Endometrial cancer

Metabolic syndrome like obesity and hyperglycemia is related to the development of endometrial cancer. Metformin is an effective anti-diabetic drug, studies have demonstrated the beneficial effect of metformin on endometrial cancer development by the mechanisms involving the mitochondrial OXPHOS suppression and AMPK activation which subsequently inhibit a variety of metabolic pathways, including STAT3, ZEB-1, ACC, mTOR, and IGF-1 [81].

1.1.6.6 Melanoma

Melanoma is the most aggressive skin cancer and is responsible for almost 80% of the skin cancer-related deaths. Due to its strong invasive ability, melanoma often metastasizes to the lymph nodes, liver, lungs, and even the central nervous system [82]. Metformin can induce cell cycle arrest in the G0–G1 phase in melanoma cells. Another study indicated that metformin can attenuate melanoma growth and

metastasis through inhibiting the expression of TRB3 (tribbles pseudokinase 3) in non-diabetic and diabetic mouse models [83]. Because of the activation effect of AMPK, metformin could influence melanoma cell death and proliferation and the tumor microenvironment. It will be interesting to investigate the effects of combination treatment of metformin with current therapies or other drugs to treat melanoma.

1.1.7 Metformin in aging

Aging is considered unavoidable and is modulated by genetic and dietary factors. The declining ability to regenerate damaged tissue and the deterioration in homeostatic processes are considered as biological features of aging [84]. Usually, the primary causes foraging are DNA damage and autophagy. Aging is a result of DNA damage, which can be induced by ROS, alkylation, hydrolysis, chemicals, and ultraviolet and other radiation [85]. Trials have shown metformin's efficacy in reducing the effects of aging, such as decreasing age-related illnesses, problems with cognitive function, and morbidity [86].

Metformin slows down aging and reduces the incidence of aging-related diseases such as neurodegenerative disease and cancer in humans. In spite of its widespread use, the mechanisms by which metformin exerts favorable effects on aging remain largely unknown [87]. The mechanisms by which metformin affects the aging process are partly dependent on the regulation of glucose metabolism. By inhibiting mitochondrial complex I, metformin reduces endogenous production of ROS and subsequently decreases DNA damage [88].

By activating AMPK, metformin is able to inhibit NF-kB signaling and attenuate cell inflammation [89]. Metformin also leads to decreased insulin levels, and suppresses IGF-1 signaling and mTOR signaling, resulting in suppression of inflammation and autophagy, which is beneficial to the aging process [90]. Besides, metformin was shown to have a function in the regulation of the microbiome, which may be another way to affect aging [91]. There are three main factors that are related with aging. They are oxidation, glycation and methylation. There is evidence that metformin acts as an anti-aging agent. It helps slow the rate of aging and retain youth characteristics for a longer period of time than compared to non-metformin users. There are ongoing research about the effect of metformin on anti-aging properties. Researches have proved that metformin is linked with anti-aging factors [92].

There are two mechanisms to describe aging. First one is ROS theory, i.e., reactive oxygen species [93]. The ROS theory explains that by products of oxidative phosphorylation are reactive oxygen species, i.e., free radicals. The free radicals increase significantly and damage other cells and organs. The ROS leads to DNA damage [64].

The second mechanism is TOR theory. Cellular pathway like IGF-1 axis, MAPK, AKT, PI3K stimulated by mitogens, growth factors, sugars and amino acids are said to inhibit aging. Caloric restriction suppresses the mTOR pathway. The activity of mTOR may be inhibited by rapamycin. Rapamycin has gero-suppressive effects. These include extending the lifespan, prevent age related disorders and reduce cost of patient care. AMPK activation led to an indirect inhibition of mTOR. Metformin acts as an AMPK activator [64, 94]. Metformin, Being an AMPK activator, metformin has been proved to have gero-suppressive effects. Extended longevity and lifespan were seen in those taking metformin. Autophagy plays a significant role in gero-suppressive mechanisms. Autophagy protects cell organelles and nutrient supply. Induction of autophagy extends the lifespan. Polyamines cause autophagy. Activation of autophagy induces processes associated with suppression of IGF and mTOR pathways. Therefore metformin acts as an activator of autophagy [95].

1.1.8 Metformin in liver diseases

Liver dysfunction may lead to many diseases, such as diabetes, non-alcoholic fatty liver disease, cirrhosis, non-alcoholic hepatitis, and hepatocellular carcinoma. Studies showed that metformin is safe in patients with cirrhosis. In diabetic patients, metformin caused a 50% reduction in hepatocellular carcinoma incidence and improved survival mainly by influencing cell growth and angiogenesis through the PI3K/AKT/mTOR signaling pathway [96]. In humans, metformin was also found to reduce the incidence of fatty liver diseases and to cause a histological response [97]. However, other studies showed that metformin failed to improve liver histology, hepatic steatosis, and inflammation [98].

1.1.9 Metformin and cardiovascular diseases

Hyperglycemia induces oxidative stress, resulting in lipoprotein dysfunction and endothelial dysfunction, increasing the risk of CVD. Metformin was shown to decrease the incidence of CVD in diabetes patients. Metformin was also shown to decrease irregular heartbeats and lower oxidative stress [86]. Through activating AMPK, metformin inhibits alpha-dicarbonyl-mediated modification of apolipoprotein residues, consequently ameliorating high density lipoprotein (HDL) dysfunction and reducing low density lipoprotein (LDL) modifications. Reductions in HDL dysfunction improve cholesterol transport and diminish the cardiovascular risk. Moreover, metformin improves endothelial oxidative stress levels and attenuates hyperglycemia-induced inflammation, decreasing the occurrence of CVD [99]. It has been shown that metformin improves the myocardial energy status through ameliorating cellular lipid and glucose metabolism via AMPK [100].

1.1.10 Metformin and renal diseases

Diabetes is considered as an important cause of renal diseases, and metformin is an interesting candidate to treat renal diseases, although its use was restricted previously [101]. Daily oral administration of metformin could improve kidney fibrosis and normalize kidney structure and function. These effects may be mediated by the AMPK signaling pathway, which can regulate cell growth and energy utilization. Another study found that in a CKD mouse model, metformin could suppress kidney injury and improve kidney function, through AMPK-mediated ACC signaling [102].

It is worth to note that appropriate dosage of metformin is very important in the treatment for renal diseases. The mechanisms underlying these kidney protective roles of metformin may be related to the regulation of glucose utilization, the decrease in cell inflammation, and oxidative stress [103]. The summary of metformin in different diseases and the underlying major mechanism is shown in the **Figure 4.**

1.2 Cons (side effects) of metformin

Metformin as all drugs, have unwanted effects which can be mild or serious side effects. The most common side effects are related to gut complications and include upset stomach, nausea, vomiting, diarrhea, light headedness, or a metallic taste in the mouth [104]. In general, older patients may be at an increased risk for some of its side effects, such as lactic acidosis or low blood sugar, due to other factors [104]. The minor side effects include gastrointestinal disturbances. The most common are anorexia, nausea, abdominal discomfort and diarrhea. Dose reduction or discontinuation of the drug may reduce or alleviate these symptoms. Out of the side effects,

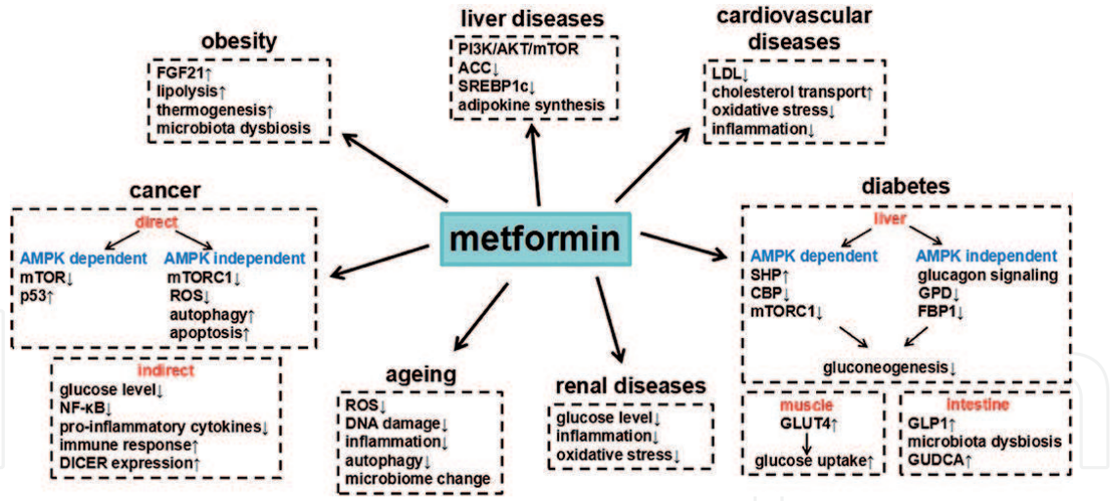

Figure 4.
Summary of metformin in different diseases and the underlying major mechanism [103].

lactic acidosis and vitamin B12 deficiency happens to be the major. Although rare, if lactic acidosis occurs, may be fatal, which may occur in presence of hypoxia and renal insufficiency [105].

1.2.1 Lactic acidosis

Lactic acidosis is a condition in which lactic acid builds up in the body, altering pH balance and potentially leading to complications [106]. Because metformin reduces the breakdown of lactate to glucose, the drug may induce lactic acidosis if it accumulates significantly. Metformin's exact mechanism of action in doing so is unknown. More frequently, the combination of this drug and an underlying health condition may trigger lactic acidosis [107].

The rate of developing lactic acidosis increases in patients with predisposing factors, such as renal impairment, hepatic disease, congestive heart failure or sepsis. Metformin is renally cleared. In cases of renal failure or decreased creatinine clearance, metformin accumulates. When this happens, it inhibits mitochondrial electron transport. Therefore, it increases anerobic metabolism and lactic production [108]. The levels of lactate increase in metformin taking patients. The pyruvate dehydrogenase inhibits conversion of lactate to glucose, thereby causes lactic acidosis [109].

Because metformin decreases liver uptake of lactate, any condition that may precipitate lactic acidosis is a contraindication. Patients with infections, recent surgery, kidney or liver damage, history of heart disease, respiratory failure, excessive alcohol consumption (due to depletion of NAD+ stores), or dehydration have an increased risk of lactic acidosis induced by metformin [110]. The FDA recommends avoiding the use of metformin in more severe chronic kidney disease, below the eGFR cutoff of 30 ml/minute/1.73 m^2.

Lactate uptake by the liver is diminished with metformin use because lactate is a substrate for hepatic gluconeogenesis, a process that metformin inhibits. Metformin-associated lactate production may also take place in the large intestine, which could potentially contribute to lactic acidosis in those with risk factors. Elderly patients are also at risk for developing lactic acidosis [104, 111].

1.2.2 Vitamin B12 deficiency

A common report with long term metformin use is vitamin B12 malabsorption which leads to vitamin B12 deficiency [112, 113]. With increased metformin

dosage, the incidence of vitamin B12 deficiency also increased [114]. In a study, it was proven that being treated with metformin had a 7% greater risk of vitamin B12 deficiency than with placebo [115].

The mechanisms leading to vitamin B12 deficiency may be explained by changes in small intestine motility. This cause increased bacterial growth and hence, consumption of vitamin B12. Metformin also inhibits the calcium dependent absorption of vitamin B12 [116]. Vitamin B12 is an essential nutrient for cognitive and cardiovascular function [117, 118]. Clinical manifestations of vitamin B12 deficiency include alteration in mental status, megaloblastic anemia and neurological damage [118].

1.2.3 Hypoglycemia

Metformin, itself, does not lead to a state of critically low blood sugar. In combination with other risk factors such as heavy alcohol drinking (or dehydration), the use of other drugs for diabetes, insufficient calorie intake, or bouts of heavy exercise, it may increase the chances of developing hypoglycemia [100]. Since metformin does not directly stimulate insulin secretion, hypoglycemia risk may be lower than for that of other oral anti-diabetes drugs. However, hypoglycemia in patients using metformin may occur in association with strenuous physical activity or fasting [119].

1.2.4 Anemia

Metformin can decrease the levels of vitamin B12 in our body. In rare cases, this can cause anemia or low levels of red blood cells. Metformin use is associated with early risk of anemia in individuals with type 2 diabetes. The mechanism for this early fall in hemoglobin is uncertain, but given the time course, is unlikely to be due to vitamin B_{12} deficiency alone [120].

Vitamin B12 (cobalamin) deficiency is a frequent cause of megaloblastic anemia that is evident through various symptoms [121]. However, the mechanism for these findings is unclear. Because development of anemia was not obviously associated with a rising mean cell volume (MCV) or macrocytosis, vitamin B12 deficiency is an unlikely explanation in most cases. We should evaluate anemia in metformin users as we would for any patient; if a thorough evaluation is unrevealing, we might cautiously attribute the anemia to metformin [120].

1.2.5 Cognitive impairments

A case–control study of over 7,000 patients with Alzheimer's disease showed that, compared to insulin treatments, sulfonylureas, and thiazolidinediones, metformin was associated with an increased incidence of Alzheimer's [122]. However, another study on approximately 1,500 people showed that the cognitive impairment associated with metformin may be alleviated with vitamin B12 and calcium supplements [123]. Controversies are seen as studies have reported that metformin was found to significantly reduce the occurrence of cognitive dysfunction in patients with T2D [124]. Several studies found that metformin improved cognitive abilities [125, 126]. The relationship between metformin and cognitive dysfunction in patients with T2D is controversial.

1.2.6 Gastrointestinal

Gastrointestinal upset is most common when metformin is first administered, or when the dose is increased. This can cause severe discomfort which can often be

avoided by starting the drug at a low dose and increasing the dose gradually, but even with low doses, 5% of people may be unable to tolerate metformin. Long-term use of metformin has been associated with increased homocysteine levels and malabsorption of vitamin B12. Higher doses and prolonged use are associated with increased incidence of vitamin B12 deficiency.

2. Conclusion

Metformin, the drug initially approved and used for the treatment of Type 2 diabetes mellitus is proven to be effective in many other conditions such as gestational diabetes mellitus, obesity, hypersecretion of ovarian androgens, poly-cystic ovary syndrome (PCOS), anti-psychotic therapy induced weight gain, cancer treatment etc. There are ongoing research about the effect of metformin on anti-aging properties and proved that metformin is linked with anti-aging factors.

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