REVIEW ARTICLE

Metformin: Current knowledge

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Diabetes mellitus is a group of metabolic disorders in which the blood glucose is higher than normal levels, due to insufficiency of insulin release or improper response of cells to insulin, resulting in high blood pressure. The resultant hyperglycemia produces sever complications. Metformin drug has been shown to prevent diabetes in people who are at high risk and decrease most of the diabetic complications. Recent reports on metformin, not only indicate some implications such as renoprotective properties have been suggested for metformin, but some reports indicate its adverse effects as well that are negligible when its benefits are brought into account. We aimed here to review the new implications of metformin and discuss about the concerns in the use of metformin, referring to the recently published papers.

Key words: Diabetes, diabetes mellitus, diabetic nephropathy, glucose, metformin, new applications, polycystic ovary syndrome, renoprotection

How to cite this article: Nasri H, Rafieian-Kopaei M. Metformin: Current knowledge. J Res Med Sci 2014;19:658-64.

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders in which the blood glucose is higher than normal levels, due to insufficiency of insulin release or improper response of cells to insulin, resulting in high blood pressure. The resultant hyperglycemia produces the classical symptoms of polyuria, polydipsia and polyphagia. It may also cause nerve problems, kidney problems, and blindness, loss of limbs, and sexual dysfunction, increase in heart attack or stroke.[1] Metformin (a biguanide derivative), by controlling blood glucose level decreases these complications. Metformin works by helping to restore the body's response to insulin. It decreases the amount of blood sugar that the liver produces and that the intestines or stomach absorb.[2] Metformin, other than hypoglycemic activity, has been taken with diet and exercise changes to prevent diabetes in people who are at high risk for becoming diabetic. It is also used in women with polycystic ovarian syndrome. Metformin may make menstrual cycles more regular and increase fertility.[3] Metformin was first synthesized and found to decrease the blood glucose level in the 1920s; however, it was not used for a long time. The use of metformin was rekindled in 1957, when the results of a clinical trial were published confirming its effect on diabetes. Metformin is now widely prescribed as an anti-diabetic drug; however, there have been serious concerns about its adverse effects, especially ketoacidosis.[4] Recently, not only some implications have been discovered for metformin, but also there are reports indicating that its adverse effects are negligible when its benefits are brought into account.[3] Theoretically, its use has been prohibited in a large group of patients with type 2 diabetes mellitus due to the risk of lactic acidosis. However, it has been shown that several diabetic patients who are considered to be at risk have received metformin with no increased risk of lactic acidosis.[2-5] Furthermore, recently some papers have been published indicating renoprotective properties for metformin. We aimed here to review the new implications of metformin and discuss about the concerns in the use of metformin, referring to the recently published papers.

NEW AND OLD IMPLICATIONS AND THE MECHANISMS OF ACTION

Diabetes mellitus

Metformin is primarily used for the treatment of type 2 diabetes mellitus, particularly in obese.patients. Metformin has been shown to reduce diabetes mortality and complications by thirty percent compared to insulin, glibenclamide and chlorpropamide.[5]

Metformin reduces serum glucose level by several different mechanisms, notably through nonpancreatic mechanisms without increasing insulin secretion. It increases the effects of insulin; hence, it is termed "insulin sensitizer". Metformin also suppresses the endogenous glucose production by the liver, which is

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Received: 24-0-2013; **Revised:** 25-12-2013; **Accepted:** 15-01-2014

mainly due to a reduction in the rate of gluconeogenesis and a small effect on glycogenolysis. Moreover, metformin activates the enzyme adenosine monophosphate kinase (AMPK) resulting in the inhibition of key enzymes involved in gluconeogenesis and glycogen synthesis in the liver while stimulating insulin signaling and glucose transport in muscles. AMPK regulates the cellular and organ metabolism and any decrease in hepatic energy, leads to the activation of AMPK. This study to an extent has put forth to explain the mechanism of metformin action on liver gluconeogenesis.[6,7]

Furthermore, metformin increases the peripheral glucose disposal that arises largely through increased non-oxidative glucose disposal into skeletal muscle. It usually does not cause hypoglycemia and this cause to be considered as a unique anti-diabetic drug.[8]

Treatment of diabetes with metformin is associated with less weight gain compared with insulin and sulfonylureas. Weight gain helps in better glucose control. In a study it was shown that, over a 10-year treatment period, the patients treated with metformin gained about one kg, the patients treated with glibenclamide gained about three kg, and the patients treated with the insulin gained six kg weight.[9]

Pre-diabetes

The chance of developing type 2 diabetes mellitus may decrease in people at risk for this disease; however, dieting and intensive physical exercise may work significantly better for this purpose. In a large study in the United States, participants were given placebo, lifestyle intervention or metformin, and followed for three years. The lifestyle modifications included a 16-lesson training on exercise and dieting followed by monthly sessions for individuals with the aim of decreasing the body weight by 7%. These patients under this group were engaged in a physical activity for about 150 minutes/week. The incidence of diabetes mellitus in this group was by 58%, and in metformin group by 31%. After ten years, the incidence of the disease was lower by 34% in the patients on diet and exercise and 18% in the metformin group.[10]

Gestational diabetes

Several trials have suggested that metformin is as safe and effective as insulin for the treatment of gestational diabetes,[11] and it has been suggested that the mothers who have used metformin instead of insulin might be healthier in the neonatal period.[12] However, evidence is still lacking on the long term safety of metformin for both children and mothers.[13]

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is frequently associated with resistance to insulin and since 1994, metformin has been proposed as a treatment for PCOS.[14] In 2004, National Institute for Health and Clinical Excellence recommended to prescribe metformin for women with PCOS and a body mass index above 25 for anovulation and infertility when other therapies have failed to produce acceptable results.[15] However, several subsequent reviews did not show promising results and did not recommend it further or at least as a first-line medication,[16] except for women with glucose intolerance.[17] The guidelines usually suggest clomiphene to be the first treatment and recommend lifestyle modification independent from drug therapy.

A systematic review using comparative trials of clomiphene and metformin found equal results for infertility[18] and A BMJ editorial suggested that metformin should be used as a second choice, if clomiphene treatment fails.[19] Furthermore, a large review using 27 clinical trials found that metformin was not associated with any increase in the number of live births; however, it improved ovulation rates, especially when it was used in combination with clomiphene.[20]

Further, a review recommended metformin as a first choice because of positive effects on insulin resistance, hirsutism, anovulation and obesity, which are often associated with polycystic ovary syndrome.[21]

The different trial designs might be the reasons for the contradictory results. For example, considering live birth rate instead of pregnancy as the endpoint might have biased a few trials against metformin.[22] Another explanation is that metformin may have different efficacy in different populations.

Cancer protection

A large case-control study has suggested that metformin might protect patients against pancreatic cancer. In this study, the risk of pancreatic cancer in metformin group was 62% lower than in placebo group who did not use metformin. The participants having sulfonylureas or insulin were found to have a 2.5-fold and 5-fold higher risk of pancreatic cancer, respectively, in comparison to placebo group.[23] Several studies have suggested that diabetic patients using metformin might lower the risk of cancer compared to those using other anti-diabetic drugs.[24,25] However, the results need confirmation in controlled trials.[26]

Metformin has shown a strong antiproliferative effects on colon, pancreatic, breast, ovarian, prostate and lung cancer cells. Preclinical studies have also shown reliable anti-tumoral effects in different animal models. A clinical trial has demonstrated beneficial effect in colon and breast cancers.[27]

The mechanism of this action is not clear. Other anti-diabetic drugs have not shown the same anticancer activities; hence, the anticancer effect of metformin should not be related to anti-diabetic activity of this drug. Metformin possesses antioxidant activity.[28] Antioxidants have been shown to have various beneficial effects such as anticancer,[29-32] antidiabetes[33] and antiatherosclerosis[34,35] properties. Therefore, some beneficial effects of metformin might be related to its antioxidant activity.

HIV-associated diabetes

The use of some of antiretroviral drugs in HIV-infection has been associated with glucose tolerance, insulin resistance, hyperinsulinemia and type 2 diabetes mellitus. Low HDL, Hypertriglyceridemia and high risk of cardiovascular diseases have been reported in these patients. These metabolic alterations are frequently associated with loss of subcutaneous fat and increased visceral fat.[36,37]

Antiretroviral therapies with protease inhibitors inhibit glucose transporter (GLUT)-4 mediated glucose transport.[38] They are likely to be, in part, responsible for the insulin resistance and body composition changes in HIV-infected patients. Metformin has been shown to reduce visceral adiposity and insulin resistance after 8 weeks of drug therapy at dose of 850 mg, 3 times per day.[39]

Nephrotoxicity prevention

Recent studies have suggested that metformin may have therapeutic or renoprotective effects against nephrotoxic agents.[40,41] It has also been shown to have a good efficacy in diabetic nephropathy.[40-44] Furthermore, it significantly decreases albuminuria in patients with diabetes mellitus.[41-44] However, the exact mechanism beyond these effects is still unknown. Recent studies have shown that therapeutic effect of metformin is mediated through its action on adenosine monophosphate (AMP)-activated kinase in tissues.[43-48] Various studies have shown that metformin is capable of decreasing intracellular reactive oxygen species (ROS).[45-49] It protects tubular injury through regulation of oxidative stress and restoring the biochemical alterations on renal tubules. Metformin may also protect the podocytes in diabetic nephropathy.[47-51]

Various studies have shown that AMPK activation of metformin is secondary to its effect on the mitochondria as the primary target.[52] Recent studies have demonstrated a direct or mediated mitochondrial effect for metformin.[53] When metformin is used alone, its beneficial effect is due to the mild inhibition of the mitochondrial respiration.[54,55]

The effect of mitochondria in programmed cell death is usually associated with the release of apoptotic signaling molecules.[56] Moreover, ROS production by mitochondria may also lead to cell degradation.[57]

Mitochondria represents as one of the major cellular sources of ROS generation,[50] and a great number of tissue pathologies, which induce oxidative stress.[58,59] These findings may show the critical role of mitochondria in these conditions.[58,59]

The nephrotoxicity of aminoglycosides and most of other renotoxic agents has been attributed to ROS.[60] In certain conditions, intracellular ROS may reach a toxic level, resulting in oxidative damage and malfunctioning of the organ.[54]

We conducted a study on male Wistar rats to test the potential properties of metformin in protecting the kidney from gentamicin-induced acute renal failure, and to find out by postponing the treatment with metformin in acute renal failure exerts similar benefits as on gentamicin nephrotoxicity in rats.[61] Metformin not only had preventive effect but also exerted ameliorative activity against gentamicin nephrotoxicity. Hence, it might be beneficial in patients under treatment with this drug.[49]

Metformin has also shown to have beneficial effect on renal function and structure after unilateral ischemia-reperfusion in rats.[62] The authors in this study have concluded that metformin has tissue protection with the activation of endothelial nitric oxide synthase and AMPK.[61]

Various studies have shown that ROS overproduction might be the key starting events, which cause development of complications of diabetes.[63] However, the exact mechanisms that cause hyperglycemia and diabetic nephropathy are not elucidated.[64] It has been shown that nucleic acids can be affected by oxidative stress, thereby modifying the bases in DNA. When DNA is damaged the affected cells start a response such as cell cycle delay, DNA repair or apoptosis induction. ROS generation by oxidative stress causes cell death.[65] Apoptosis is implicated in the pathogenesis of diabetic nephropathy. ROS is an inducer of apoptosis in various cell types including podocytes.[66]

Metformin is able to restore the podocytes in diabetic rats and diabetes-induced podocyte loss in diabetic nephropathy has been attenuated to ROS.[67] Podocyte apoptosis is associated with increased albuminuria. Phosphorylation of AMPK is reduced in the kidney of diabetic rats. Therefore, metformin may exert some of its effects by improving the renal oxidative stress.[67] These findings are in agreement with other studies showing beneficial antioxidant properties of metformin in diabetic rats.[68]

These findings may encourage the clinical use of metformin along with nephrotoxic drugs as well as for prevention of diabetic nephropathy.

Side effects

Metformin has not significant adverse effects; however, it may cause a serious condition called lactic acidosis with the following symptoms: Dizziness, severe drowsiness, muscle pain, tiredness, chills, blue/cold skin, fast/difficult breathing, slow/irregular heartbeat, stomach pain with diarrhea, nausea or vomiting.[1,41,43,69]

Lactic acidosis usually occurs due to drug overdose or in some contraindicated conditions. It is more likely to occur in patients with certain medical conditions, including a serious infection, liver or kidney disease, recent surgery, any conditions that cause a low level of oxygen in the blood or poor circulation (such as recent stroke, congestive heart failure, recent heart attack), heavy alcohol use, dehydration, X-ray or scanning procedures that require an injectable iodinated contrast drug and those older than 80 years.[1,41,43,70]

Nausea, vomiting, stomach upset, diarrhea, weakness, or a metallic taste in the mouth may occur.

Metformin usually does not cause hypoglycemia; however, low blood sugar may occur if this drug is used with other anti-diabetic drugs. Hypoglycemia is more likely to occur with heavy exercise, drinking large amounts of alcohol, or not consuming enough calories from food.

Symptoms of hyperglycemia include polydipsia, polyuria, rapid breathing, flushing, confusion, drowsiness, and fruity breath odor.[1,41,43,71,72]

Serious allergic reaction to this drug is rare; however, this product may contain inactive ingredients, which can cause allergic reactions or other problems. High fever, diarrhea, vomiting, diuretics or excess sweating may cause dehydration and increase the risk of lactic acidosis. Older adults may be at greater risk for side effects such as low blood sugar or lactic acidosis.[1,41,43,62,71]

Gastrointestinal intolerance is one of the most frequently occurred and lactic acidosis is a rare, but causes serious adverse effects.[73,74] Incidence of myocardial infarction (MI) is also an important event but seen less in metformin compared with sulfonylurea agents.[75] Metformin induced lactic acidosis is a rare but important and fatal adverse event.

A population-based study demonstrated that about one-fourth of patients prescribed metformin had contraindications to its use. However, contraindications rarely resulted in discontinuation of metformin usage.[76] These data have been confirmed by several other studies in different countries.[77,78]

Furthermore, in a recent review article, based on 347 observational cohort studies and prospective comparative trials, no evidence indicating metformin to be associated with increased levels of lactate or increased risk of lactic acidosis in comparison to other antihyperglycaemic drugs has been reported.[7-79] It should be noted that in this report, all clinical trials excluded the risk patients. Therefore, the scenario might be rather different, in real population.

In a study sample of 19,691 type 2 diabetes mellitus (DM), patients with established atherothrombosis participating in study, the two-year mortality rate was significantly less in patients treated with metformin compared with the patients not treated with metformin.[80,81]

Therefore, it might be necessary to reconsider the list of contraindications in the use of metformin.

However, considering the high prevalence of stable renal impairment, congestive heart failure and/or coronary artery disease in elderly patients, the benefit-risk balance of metformin treatment are of particular important and more valuable data especially relevant to the elderly population are still required. In this regard, benefit-risk ratios are needed without deprivation of patients at risk.

METFORMIN DURING PREGNANCY AND LACTATION

It has been shown that pregnancy may alter the function of drug-metabolizing enzymes and drug transporters in a gestational stage. The activities of several hepatic cytochrome P450 enzymes such as CYP2D6 and CYP3A4 are increased, whereas the activity of some others, such as CYP1A2, may be decreased. The activities of some renal transporters, including organic-cation transporter and P-glycoprotein increase during pregnancy. However, significant gaps still exist in our understanding of the spectrum of drug metabolism and transport genes affected, gestational age-dependent changes in the activity of encoded drug metabolizing and transporting processes, and the mechanisms of pregnancy-induced alterations.[52,82]

The pharmacokinetics of metformin is also affected by pregnancy, which is related to the changes in renal filtration and net tubular transport, which can be estimated roughly by the use of creatinine clearance. At the time of delivery, the fetus is exposed to variable concentrations of metformin from negligible to as high as maternal concentrations. However, infant exposure to metformin through the breast milk is low.[83]

Metformin appears to be effective and safe for the treatment of gestational diabetes mellitus, particularly for overweight or obese women. It has been suggested

that metformin is safe during pregnancy. However, as metformin crosses the placenta, its use during pregnancy raises concerns regarding potential adverse effects on the mother and fetus. Furthermore, patients with multiple risk factors for insulin resistance may not meet their treatment goals with metformin alone and may require supplementary drugs such as insulin. However, there are potential advantages for the use of metformin over insulin in gestational diabetes mellitus with respect to maternal weight gain and neonatal outcomes. Furthermore, the use of metformin throughout pregnancy in women with polycystic ovary syndrome decreases the rates of early pregnancy loss and preterm labor; hence protecting against fetal growth restriction. There have been no demonstrable teratogenic effects, intrauterine deaths or developmental delays with the use of metformin. Therefore, the evidence supports the efficacy and safety of metformin during pregnancy with respect to immediate pregnancy outcomes. However, because there are no guidelines for the continuous use of metformin in pregnancy, the duration of treatment is based on clinical judgment and experience on a case-by-case basis.[84-89] Recently, the Endocrin Society has not only confirmed the use of metformin during pregnancy but also has recommended it as a first-line treatment of cutaneous manifestations, for prevention of pregnancy complications, or for the treatment of obesity.[85,86] It should be noted that not all references allow the use of metformin in the first trimester of pregnancy.[90] Therefore, it is suggested that metformin therapy be used for glycemic control only for those women with gestational diabetes who do not have satisfactory glycemic control despite medical nutrition therapy and who refuse or cannot use insulin or glyburide in the first trimester.

CONCLUSION

Metformin is an oral anti-diabetic drug in the biguanide class for the treatment of type 2 diabetes mellitus, in particular, in overweight and obese people and those with normal kidney function.

Metformin has several benefits in patients with type 2 diabetes mellitus, including decreased hyperinsulinemia, weight reduction, augmented fibrinolysis, improved lipid profiles and enhanced endothelial function.

Although the use of metformin in diabetes has its safety concerns, its benefits and the recent results indicate that the nephroprotective activity against nephrotoxic agents on metformin and its recent good safety records have led researchers to consider the use of this drug more and more in insulin resistant states even before the development of hyperglycemia.

AUTHORS' CONTRIBUTIONS

All authors have contributed in designing the study. Both of them have assisted in preparation of the first draft of the manuscript or revising it critically for important intellectual content. They have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

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Source of Support: Nil, **Conflict of Interest:** None declared.