Review Article

Metformin beyond hypoglycemic effect

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Abstract
Metformin is a biguanide belongs to a class of insulin sensitizers. The drug is widely used for the treatment of type 2 diabetes mellitus. Metformin was introduced in clinical practice to treat the individuals with diabetes. Furthermore, metformin’s effect has other markers beside its insulin-sensitizing action. The present review is aimed at describing all evidence-based and potential uses of metformin in individuals. In particular, we have analyzed the use of metformin not only for the treatment of type II diabetes but also complicated pregnancy risk, hyperandrogenism, endometrial, metabolic and cardiovascular abnormalities. The landscape of the multifaceted therapeutic effect of metformin evolves to broaden the therapeutic implications of this old drug in a new style for individuals. Most recently, the spectrum of metformin's targets has been expanded, and molecular studies have explored the tissue-specific mechanisms of metformin in the liver, the muscle, the endothelium, and the ovary. The use of metformin comprises another scarcely explored, but promising area of research. This review attempts to cover the current literature regarding the potential medical value of this medication. Even if many of these actions are individually modest, they seem to be collectively sufficient to confer therapeutic benefits not only in diabetes aspects but also in cardiometabolic and reproductive aspects also
Introduction

Diabetes mellitus is a silent disease of insidious. Type 2 diabetes is a life threatening, health hazard in most part of the world. Globally, prevalence of diabetes is 285 million among adults aged 20–79 years. By 2030, an increase of 7.7% is estimated with 439 million (Fig1).\(^1\)

![Fig 1: Prevalence of type 2 diabetes in millions](image)

Metformin is a biguanide (Fig 2) currently prescribed as an oral antihyperglycemic agent. Metformin was introduced in the market during 1957, and United States recommended only during 1995. Till date, metformin is approved by the U.S. Food and Drug Administration (USFDA) to treat type 2 DM, and the safety profile is probably superior than those seen with other insulin-sensitizing drugs.\(^2\)

![Fig 2.Biochemical struture of 1,1-dimethylbiguanide hydrochloride](image)

Metformin (dimethyl-biguanide) is an effective oral antidiabetic drug with decreased hepatic glucose production. The drug also increases the peripheral glucose uptake in skeletal muscles. Metformin is a drug of choice for the treatment of overweight and obese type 2 diabetic patients. Selective pathophysiological approach is seen with metformin by its effect on insulin resistance.

Metformin has a multiple biological effects showing platelet antiaggregating effects. Reduces the rate of formation of advanced glycation end products (AGEs) and decrease the cellular oxidative reactions. Hence, demonstrating the antioxidant effects of the drug, explaining its vascular protective effect. Studies have also stated the favorable effect of metformin on body weight, insulin resistance, hyperinsulinaemia, lipid parameters (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides), arterial hypertension, fibrinolysis, endothelial dysfunction. Henceforth, metformin appears to have a wide set of pharmacological properties, devising the drug potentially applicable even in nondiabetic patients. Individuals
include situations such as obesity, extreme insulin resistance with acanthosis nigricans, polycystic ovary syndrome also. Metformin has been proven in the Diabetes Prevention Program to be a drug with outstanding potential in preventing the conversion of IGT to type 2 diabetes. Henceforth, metformin appears to be a potential drug with multiple therapeutic effects far beyond its effect on lowering blood glucose in diabetes. The 

**Beneficial in glycemic control**

A study conducted by Mourao-Junior stated that metformin administered twice daily improved the glycemic control in type II diabetes with metabolic syndrome. Better sensitivity of insulin action is seen with metformin leading to inhibition of hepatic gluconeogenesis. Studies have also shown the WC reduction. HbA1C levels were below 8% in half of the individuals, 14% reached the ideal metabolic control (A1C up to 7%), and 47% patients showed A1C above 8%. 

Table 1. Comparison of clinical and laboratory variables before and 6 months after the introduction of metformin

![Table 1](image)

**Anti-Atherosclerotic effect beyond glucose lowering**

Type 2 diabetes is interlinked with considerable increase in cardiovascular mortality. Need to reduce the progression of atherosclerosis along with lowering blood glucose levels is to be considered effectively. Ideally, pharmacological treatment should address both of these needs. Oral antidiabetic agents exert anti-atherosclerotic effect. Metformin has showed success in reducing cardiovascular morbidity and mortality and exerting beneficial effects on lipids. Interestingly, some of these beneficial effects appear to be independent of the antidiabetic action. Therefore, author concluded that metformin is now emerging as useful drug for the attenuation of the atherosclerotic activity and for the protection of the vasculature in individuals with type 2 diabetes.

Metformin results with favourable effect on cardiovascular risk associated with type II diabetes. Blood pressure reduced by 3.6 mmol/l in the high-dose and 0.5 mmol/l in the low-dose patients over the 6-month study. HbA1c and plasma insulin fell in both the treatment groups. Triglyceride and cholesterol levels were decreased with high-dose metformin. The effects on glycemic control and lipids showed dose-dependent with metformin.
Protective effect of lipid accumulation in metabolic syndrome

Metformin shows reduced effect on lipid accumulation in macrophages by repressing FOXO1-mediated FABP4 transcription. Metformin has a protective effect against lipid accumulation in macrophages and may serve as a therapeutic agent for preventing and treating atherosclerosis in metabolic syndrome. The antidiabetic drug metformin has reported to reduce lipid accumulation in adipocytes.

Metformin significantly reduced palmitic acid (PA)-induced intracellular lipid accumulation in macrophages. Metformin further promoted the expression of carnitine palmitoyltransferase I (CPT1), while reducing the expression of fatty acid-binding protein 4 (FABP4) involved in PA-induced lipid accumulation. PCR showed that metformin modulates FABP4 expression at the transcriptional level. We identified forkhead transcription factor FOXO1 as a positive regulator of FABP4 expression. Inhibiting FOXO1 expression with FOXO1 siRNA significantly reduced basal and PA-induced FABP4 expression. Overexpression of wild-type FOXO1 and constitutively active FOXO1 significantly increased FABP4 expression, whereas dominant negative FOXO1 dramatically decreased FABP4 expression. Metformin decreased FABP4 expression by promoting FOXO1 nuclear exclusion and subsequently restricting its activity.10

Myocardial infarction risk decreases with metformin

Cardiovascular effects seen in type 2 diabetes (T2DM) is a major issue in clinical practice. Risk of myocardial infarction (MI) in patients affected by T2DM without previous cardiac events is similar to that of non-diabetic individuals with previous MI. Tight glycemic control and aggressive therapy is required to reduce the elevated cardiovascular risk associated with T2DM. United Kingdom Prospective Diabetes Study (UKPDS) showed that in obese type 2 diabetic patients metformin reduces the risk of MI more than sulphonylureas or insulin. Vasoprotective role of metformin is largely autonomous of its hypoglycemic action and has been attributed to pleiotropic effects. Putative beneficial action exerted by metformin on arterial vessels by evaluating its effects on lipids, inflammation, hemostasis, endothelial and platelet function and vessel wall abnormalities has been considered. Henceforth, the molecular mechanisms of the beneficial metabolic and vascular effects of metformin is be considered, with a particular attention for its ability to activate AMP-activated protein kinase.11

Metformin in GDM

Metformin belongs to category B drug indicated there is no evidence of fetal or animal teratogenicity but there are legitimate concerns about metformin use in pregnancy.12 A pilot study was conducted on metformin use in pregnant women with polycystic ovarian syndrome. Results showed that metformin therapy had no teratogenicity and reduced high rate of first trimester abortion among women.13
In MiG trial, out of 363 individuals assigned with metformin, 92.6% continued to receive metformin until delivery and 46.3% received supplemental insulin. Therefore, metformin may have an adjunct role to insulin which may be important in those pregnant females with marked insulin resistance. Metformin showed a continuous benefit in pregnancy with significant reduction in cardiovascular events.

**Fig 3. Metformin v/s Insulin in Pregnant women**

**Metformin: Decreases androgen levels in PCOS**
Metformin has shown beneficial in reducing hyperinsulinaemia and hyperandrogenaemia in PCOS patients. Metformin improves insulin response during the oral glucose tolerance. Insulin sensitizers like metformin act directly on the thecal cells decreasing steroid production. Attia et al. concluded that metformin had direct inhibitory effect on androstenedione production in human ovarian thecal like androgen-producing tumour cells. Henceforth, these findings explains the mechanism for decrease in androgen levels with metformin.

**Neuroprotective Role of Antidiabetic Drug :Metformin**
Oxidative damage occurs in pathogenesis of diabetic neuropathy and neurodegenerative diseases. Oral antidiabetic drug, metformin prevents oxidative stress-related cellular death in non-neuronal cell lines. In this study, author pointed the direct neuroprotective effect of metformin, using the etoposide-induced cell death model. The exposure of intact primary neurons to this cytotoxic insult induced permeability transition pore (PTP) opening, the dissipation of mitochondrial membrane potential (ΔΨm), cytochrome c release, and subsequent death. Importantly, metformin in combination with cyclosporin A (CsA), strongly extenuate the activation of apoptotic cascade. In addition, metformin delays CsA-sensitive PTP opening in permeabilized neurons, as a trigger by a calcium overload, probably through its mild inhibitory effect on the respiratory chain complex I. Author concluded that etoposide-induced neuronal death is partly attributable to PTP opening and the disruption of ΔΨm with the emergence of oxidative stress and metformin inhibits this PTP opening-driven commitment to death. Thus, results proposed that metformin, beyond its antihyperglycemic role, also acts as a effective drug for diabetes-associated neurodegenerative disorders.
**Metformin: Decrease oxidative stress and platelet activation**

In type 2 diabetes, metformin reduces cardiovascular risk beyond the effect of glycaemic control. Oxidative stress and enhanced platelet activation contribute to accelerated atherosclerosis in diabetes. Formosa and his colleagues conducted a randomized trial to find out the blood glucose, insulin, HbA(1c), vitamin A and E levels, 2 alph and 11-dehydro-thromboxane B and urinary excretion. Study was carried out in 26 newly diagnosed type 2 diabetics for 12 weeks. Study reported that urinary excretion was decreased. Vitamin A and E levels increased significantly in metformin group. Authors concluded that metformin improves oxidative stress, preserve antioxidant function and restrain platelet activation in type 2 diabetes\(^\text{18}\).

**Antitumor effect of metformin**

Metformin is a effective antidiabetic drug with a potential new indication for the management and chemoprevention in cancer. Metformin activates AMPK inase by two separate mechanisms, the inhibition of oxidative phosphorylation/electron transport and resulting decrease in the ATP/AMP ratio and/or the direct activation of LKB1. Add-on to the inhibitory effects on protein synthesis – via inhibition of mTOR – the activation of AMPK may advance the generation of memory CD8 T lymphocytes and suppress cancer cachexia signals in the hypothalamus. Inhibition of electron transport may be a lethal insult to cancer cells (Fig 4). Metformin shows increased memory CD8 T cells and in consequence it significantly improved the efficacy of an experimental anti-cancer vaccine.\(^\text{19}\)

![Figure 4. Antitumor mechanisms of metformin action](image)

**Metformin: Reduces neoplastic cell growth in Breast cancer**

Metformin exerts pleiotropic effects that could enhance the effectiveness of available hormonal therapies. Study was conducted to find several aspects of hormonal therapy in women and examine the effectiveness of metformin. Wild-type (wt), TAM-resistant (TAM-R), and long-term estradiol-deprived (LTED) MCF-7 cells, as a model of aromatase inhibitor resistance, were grown in the presence or absence of tamoxifen or metformin for 5 days. Here, the cell growth was evaluated. Cells were grown for 48 h for immunoblot analysis and aromatase activity measurements.
Study showed that wild-type and LTED cells were equally sensitive to the growth inhibitory effects of TAM and MF, while TAM-R cells were less sensitive to TAM than to metformin. TAM-R and LTED showed additive effect with cell number increase in tamoxifen and metformin combination. Therefore, these findings suggested a major component of apoptosis in the growth inhibitory effect. ER-alpha was decreased in wt MCF-7 cells influencing the possible involvement of compound in estrogen signaling. Combination of tamoxifen and metformin reduced neoplastic cell growth. Therefore, author concluded that loss of sensitivity to tamoxifen and estrogen deprivation were seen with breast cancer response to metformin alone or in combination of metformin and tamoxifen.

**Conclusion:**

Metformin is an appropriate first-line medication. Most recently, the spectrum of metformin's target site has been expanded to include the endothelium and the ovary. Even if many of these actions are individually modest, they seem to be collectively sufficient to confer therapeutic benefits not only in cardiometabolic views but also in reproductive aspects related with insulin-resistant and proinflammatory states. In 50 years of its clinical use, there were no major risk related in metformin and the risk of serious adverse events attributable to metformin appears to be very low provided that contraindications are considered.

**References:**


