Metformin: Beyond Glycemic Control

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INTRODUCTION

Type 2 Diabetes Mellitus is a grave health hazard in most parts 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 (Fig. 1).

Metformin (dimethyl-biguanide) is an effective oral antidiabetic drug which decreases 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 multiple biological benefits including platelet antiaggregating effect. It reduces the rate of formation of advanced glycation end products (AGEs) and decreases the cellular oxidative reactions. There is also a demonstrable antioxidant action of the drug explaining its vascular protective effect. In addition, studies have stated the favourable effect of metformin on body weight,
insulin resistance, hyperinsulinaemia, lipid parameters (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides), arterial hypertension, fibrinolysis and endothelial dysfunction. Hence, metformin appears to have a wide set of pharmacological properties making the drug potentially applicable even in non-diabetic situations such as obesity, extreme insulin resistance with acanthosis nigricans, polycystic ovarian syndrome etc. 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 Mellitus. In a nutshell, therefore, metformin appears to be a potential drug with multiple therapeutic effects far beyond its effect on lowering blood glucose in diabetes mellitus thus qualifying a discussion on “Metformin-beyond glycemic control”.

**Antihyperglycemic Efficacy of Metformin**

Metformin acts by enhancing the action of insulin, especially in the liver and skeletal muscle. Meta-analyses have confirmed that the blood glucose-lowering efficacy of metformin is at least equivalent to that of other commonly used classes of antidiabetic therapy. Other than insulin, generally regarded as the most effective antidiabetic therapy, the efficacy of metformin and sulphonylureas is comparable (expected HbA1c reductions of 1-2% as monotherapy) with somewhat lower effects expected from other classes.

A study conducted by Mourao-Junior stated that metformin administered twice daily improved the glycemic control in Type 2 Diabetes with metabolic syndrome.4,5 (Table I) Better sensitivity of insulin action is seen with metformin leading to inhibition of hepatic gluconeogenesis. Studies have also shown waist circumference (WC) reduction.6 HbA1C levels were below 8% in half of the individuals, 14% reached the ideal metabolic control (A1C up to 7%) and 47% showed A1C above 8%.7

**Anti-Atherosclerotic effect of Metformin beyond glucose lowering**

Type 2 Diabetes Mellitus 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. Metformin has shown success in reducing
cardiovascular morbidity as well as mortality and exerting beneficial effect on lipids. Interestingly, some of these beneficial effects appear to be independent of the antidiabetic action. Therefore, metformin is now emerging as a useful drug for the attenuation of atherosclerotic activity and for protection of vasculature in individuals with Type 2 Diabetes.8

There is evidence of Metformin having a favourable effect on cardiovascular risk associated with Type 2 Diabetes. Blood Glucose 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-dependence with metformin.9

Role of Metformin in Obesity
Metformin is considered as a first-line drug in overweight diabetic patients. The use of metformin can significantly control the associated cardiovascular risk factors in patients suffering from Type 2 Diabetes and obesity.27 Studies have reported modest weight reduction in patients taking metformin. However, in the absence of insulin resistance or diabetes, it cannot be used as a weight-loss agent. Its anorectic property also contributes to weight loss.24

Anti-hypertensive effect of Metformin
A few reports have documented a reduction in blood pressure during therapy with metformin, either in systolic or diastolic pressure alone or in both phases. On the contrary, a few reports have documented lack of effect of metformin on blood pressure.24 Long-term infusion with apparently nontoxic doses of metformin attenuates hypertension and decreases the hypotensive responses to ganglionic blockade in salt-induced hypertensive response (SHR) suggesting a centrally elicited sympathoinhibitory action.25 In humans, however, metformin treatment is associated with a significant improvement in cardiac sympathovagal balance but not in mean arterial BP.26 Long-term research may provide us some more information on this aspect.

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 been reported to reduce lipid accumulation in adipocytes.

Metformin was found to significantly reduce palmitic acid (PA)-induced intracellular lipid accumulation in macrophages. Metformin further promoted the expression of carnitine palmitoyltransferase I (CPT-1) 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. Forkhead transcription factor FOXO1 was identified as a positive regulator of FABP4 expression. Inhibiting FOXO1 expression with FOXO1 siRNA significantly reduced basal and PA-induced FABP4 expression. Over-expression of wild-type FOXO1 and constitutively active FOXO1 significantly increased FABP4 expression whereas dominant negative FOXO1 dramatically decreased FABP4 expression. Metformin

| Table I: Comparison of clinical and laboratory variables before and 6 months after the introduction of metformin |
|---------------------------------|---------------------------------|
| Variable                        | Before                          | After                           |
| A1C (%)                         | 9.65 ± 1.03                     | 8.18 ± 1.01                     |
| FBG (mg/dL)                     | 215.3 ± 28.0                    | 167.2 ± 27.3                    |
| Daily insulin dose (IU kg\(^{-1}\) day\(^{-1}\)) | 0.83 ± 0.39                     | 0.69 ± 0.36                     |
| BMI (kg/m\(^{2}\))             | 30.7 ± 5.4                      | 29.0 ± 4.0                      |
| Waist circumference (cm)        | 124.6 ± 11.7                    | 117.3 ± 9.3                     |
| Total cholesterol (mg/dL)       | 229.0 ± 29.5                    | 214.2 ± 25.0                    |
| HDL cholesterol (mg/dL)         | 37.5 ± 8.4                      | 38.0 ± 6.3                      |
| Triglycerides (mg/dL)           | 236.2 ± 40.2                    | 218.5 ± 42.4                    |
| Systolic blood pressure (mmHg)  | 158 ± 25                        | 156 ± 18                        |
| Diastolic blood pressure (mmHg) | 92 ± 11                         | 90 ± 14                         |

**Table I: Comparison of clinical and laboratory variables before and 6 months after the introduction of metformin**

**HbA1C**

- Before Met: 9.65 ± 1.03
- After Met: 8.18 ± 1.01
decreased FABP4 expression by promoting FOXO1 nuclear exclusion and subsequently restricting its activity. Metformin reduces the risk of Myocardial Infarction
Cardiovascular effects seen in Type 2 Diabetes Mellitus (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 antihyperglycemic 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 abnormalities has been considered. Henceforth, the molecular mechanisms of the beneficial metabolic and vascular effects of metformin are to be considered with a particular attention for its ability to activate AMP-activated protein kinase.

Role of Metformin in Diabetes Prevention
The potential of metformin to prevent or delay the onset of Type 2 Diabetes in at-risk populations has been demonstrated conclusively by randomised trials including the Diabetes Prevention Program in the USA (31% risk reduction versus placebo), the Indian Diabetes Prevention Programme (26-28% versus no treatment) and a study in China (77% risk reduction versus no treatment). Meta-analyses have also found significant reductions in the risk of diabetes in at-risk metformin-treated subjects of 35-40% compared with appropriate control groups. Both the ADA and the International Diabetes Federation (IDF) include recommendations on the use of metformin within their policies for diabetes prevention.

Metformin in GDM
Metformin belongs to category B drugs indicated with no evidence of fetal or animal teratogenicity but there are legitimate concerns about metformin use in pregnancy. A pilot study was conducted on metformin use in pregnant women with polycystic ovarian syndrome. Results showed that metformin therapy had no teratogenicity and it reduced high rate of first trimester abortion among women.

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 is important in case of 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](image)

**Metformin: Decreases androgen levels in PCOS**
Metformin has been shown to be 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. Hence, these findings explain the mechanism for decrease in androgen levels with metformin.

**Neuroprotective Role of 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 a recent study, authors pointed out the direct neuroprotective effect of metformin using etoposide-induced cell death model. The exposure of intact primary neurons to this cytotoxic insult induced permeability transition pore (PTP) opening, dissipation of mitochondrial membrane potential (∆Ψm), cytochrome c release and subsequent death. Importantly, metformin in combination with cyclosporin A (CsA) strongly extenuates 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. The study concluded that etoposide-induced neuronal death is partly attributable to PTP opening and disruption of ∆Ψm 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 an effective drug for diabetes-associated neurodegenerative disorders.\(^{17}\)

**Metformin decreases oxidative stress and platelet activation**

In Type 2 Diabetes, metformin reduces cardiovascular risk beyond the effect of glycemic 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 vitamin E levels, 2 alph and 11-dehydro-thromboxane B 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, preserves antioxidant function and restrains platelet activation in Type 2 Diabetes.\(^{18}\)

**Antitumor effect of metformin**

Metformin is an effective antidiabetic drug with a potential new indication for the management and chemoprevention in cancer. Metformin activates AMPKinase 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 improves the efficacy of an experimental anti-cancer vaccine.\(^{19}\)

**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 out 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 hours 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

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**Fig.4: Antitumor mechanisms of metformin action**

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reduced neoplastic cell growth. Study 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.20

CONCLUSION
Metformin is an appropriate first-line medication not only for glycemic control but beyond this in other situations as well. Most recently, the spectrum of metformin’s target site has 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 but also in reproductive aspects related with insulin-resistant and proinflammatory states. In 50 years of its clinical use, there have been no major risks reported with metformin and the serious adverse events attributable to metformin appear to be very low provided that the contraindications are considered.

Metformin and its beneficial effects

REFERENCES