Metformin therapy: Benefits beyond glycemic control

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Metformin reduces the macrovascular complications of diabetes by improving vascular endothelial functions and reducing pro-inflammatory cytokines and oxidative stress. This can reduce cardiovascular events in patients with type 2 diabetes. It also finds place in the treatment of numerous clinical conditions other than type 2 diabetes mellitus.

KEY WORDS: Metformin, cardiovascular, obesity, polycystic ovary syndrome

Metformin is the most commonly prescribed oral antidiabetic drug in the world, which primarily helps by lowering blood glucose levels and preventing insulin resistance by virtue of its hepatoselective insulin-sensitizer action.[1] Recently, benefits in the macrovascular complications of diabetes have been attributed to it. It also finds place in the treatment of many clinical conditions other than type 2 diabetes mellitus (DM). This makes metformin offer many advantages over the currently available other oral hypoglycemic drugs. The present review addresses all the new uses of this old drug.

Metformin in Type 2 DM

Metformin is regarded as the first-line treatment in type 2 DM. It primarily reduces hepatic gluconeogenesis, i.e., decreases hepatic glucose production and increases insulin action in muscle and fat. A variety of possible mechanisms have been now demonstrated, including phosphorylation of insulin receptor and insulin receptor substrate-2 and activation of pyruvate kinase. Metformin therapy may restore the activity of enzyme system involved in the intracellular insulin-signaling cascade. It has been recently shown to stimulate 'adenosine monophosphate'-activated protein kinase, which inhibits hepatic glucose production. It is associated with a decrease in the fasting blood glucose (50–70%), fasting insulin levels, BMI and serum leptons. It causes significant improvement in $HbA1_C$ (1.5–2%) and improves lipid profile without causing weight gain. Thus, metformin is used as a therapeutic agent of first choice for monotherapy of the typical overweight patient with type 2 DM and low risk of metabolic acidosis who exhibits mild to moderate hyperglycemia and as adjunctive therapy for patients poorly controlled on sulfonylureas or thiazolidinediones.[1]

It is usually well tolerated. The most common side effects are minor gastrointestinal upset and a metallic taste. Lactic acidosis, reduced serum B_{12} levels, megaloblastic anemia and cholestatic jaundice can occur rarely. It must be avoided in patients with cardiac failure, hepatic dysfunction and renal impairment.[1]

Metformin and Cardiovascular Functions

Improves vascular endothelial functions

Metformin improves vascular endothelial function and reduces adverse cardiovascular events in patients with type 2 diabetes, although its mechanisms remain unknown. But recently it has been shown to significantly increase eNOS Ser1179 phosphorylation, nitric oxide bioactivity, with a reduction in over-expression of adhesion molecules and endothelial apoptosis caused by high-glucose exposure. It also improves vascular endothelial function in diabetes by increasing AMPK-dependent, hsp90-mediated eNOS activation.[2] Endothelial dysfunction has relevance to the pathogenesis, progression and prognosis of a wide spectrum of cardiovascular diseases. Hence these actions of metformin may be beneficial in cardiovascular

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complications of diabetics.

Vascular anti-inflammatory

Accumulating evidence suggests that inflammatory processes participate in type 2 diabetes and its atherothrombotic manifestations. Metformin dose-dependently inhibits interleukin (IL)-1beta-induced release of the pro-inflammatory cytokines IL-6 and IL-8 in human vascular smooth muscle cells (SMCs), macrophages and endothelial cells. Metformin diminishes IL-1beta-induced activation and nuclear translocation of nuclear factor kappa B (NF-kappaB) in SMCs. Furthermore, metformin suppresses IL-1beta-induced activation of the pro-inflammatory phosphokinases Akt, p38 and Erk activity. Thus, metformin can exert a direct vascular anti-inflammatory effect by inhibiting NF-kappaB through blockade of the PI3K-Akt pathway. These novel anti-inflammatory actions of metformin explain in part the apparent clinical reduction produced by metformin of cardiovascular events, not fully attributable to its hypoglycemic action.[3]

Metformin prevents oxidative stress

Hyperglycemia-induced oxidative stress is detrimental to endothelial cells, contributing to the vascular complications of diabetes. The mitochondrial permeability transition pore (PTP) is an 'oxidative stress'-sensitive channel involved in cell death. Elevated glucose concentration leads to an oxidative stress that favors PTP opening and subsequent cell death in several endothelial cell types, and metformin prevents this 'PTP opening'-related cell death.[4] It significantly decreases radical oxygen species production in cells grown in hyperglycemic medium.[5] Oxidative stress mediates atherosclerotic dysfunction; and therefore, it is assumed that these antioxidant properties of metformin may be useful in preventing atherosclerotic dysfunction in patients of diabetes.

Hypertension

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 a lack of effect of metformin on blood pressure.[1] 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.[6] In humans, however, metformin treatment is associated with a significant improvement in cardiac sympathovagal balance but not in mean arterial BP.[7] Long-term research may provide us some more information on this aspect.

Atherosclerosis

Cardiovascular disease is the major determining factor of morbidity and mortality in type 2 DM patients. The established relationship between type 2 DM and atherosclerosis has fueled suggestions that antidiabetic drugs with beneficial effects on cardiovascular risk factors may help attenuate the atherosclerotic process in diabetic patients. Protective effect of metformin on experimental atherosclerosis has been suggested in one of the studies.[8] Similarly, various *in vivo* and *in vitro* experimental evidences on the antiatherogenic properties of metformin are available.[9] A reduction in fibrinogen levels, increased activity of fibrinolytic system as well as diminished platelet aggregation, plasminogen activator inhibitor-1 activity and levels of C-reactive protein possibly account for reduced atherosclerosis process.[1]

Heart failure

Metformin should not be given to patients with heart failure because of concerns of lactic acidosis. But in one of the studies, metformin, alone or in combination, in subjects with heart failure and type 2 diabetes has been found associated with lower morbidity and mortality compared with sulfonylurea monotherapy.[10] However, there is scarcity of data supporting this effect.

Diabetic Dyslipidemia

Patients with diabetes mellitus have a 2- to 4-fold increased risk of atherosclerotic cardiovascular, peripheral vascular and cerebrovascular disease, which are the leading causes of morbidity and mortality in this population. Epidemiological studies have shown an association between diabetic dyslipidemia – which is characterized by hypertriglyceridemia; low levels of high-density lipoprotein cholesterol; postprandial lipemia; and small, dense low-density lipoprotein cholesterol (LDL-C) particles – and the occurrence of cardiovascular disease. Metformin and thiazolidinediones can be useful for the treatment of diabetic dyslipidemia.[11] Metformin produces favorable changes in HDL and LDL sub-fractions compared with gliclazide in overweight type 2 diabetic patients. Such changes may be associated with reduced atherosclerosis risk.[12] In another study, the decrease in HbA_{1c} has been shown to decrease total cholesterol and triglycerides, while no significant change has been observed in HDL and LDL cholesterol.[13]

Obesity

Obesity is the most important risk factor to develop diabetes, and 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.[14] 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.[1]

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS), with an incidence of 5% in women of reproductive age, is defined as the presence of oligomenorrhea or amenorrhea in combination with hyperandrogenism. Most patients also suffer from impaired insulin action (insulin resistance). PCOS thus resembles the metabolic syndrome. Recent data indicate that women affected by the PCOS are at greater risk for cardiovascular disease and that metformin may improve the metabolic alterations in these patients. A 6-month course of metformin improves endothelial structure and function in young, normal-weight women with PCOS. High-density lipoproteins and the ratio of 'area under curve for glucose' to 'area under curve for insulin' also significantly increase, whereas low-density lipoproteins and plasma endothelin-1 levels significantly reduce.[15] Similarly, in another study, PCOS-affected women have been found to exhibit endothelial dysfunction compared with controls, which reversed within 6 months after metformin administration.[16] Hahn *et al*.[17] reported in their study that metformin treatment ameliorates acne, hirsutism score; and restarts normal menstrual cycles in 66.7% of PCOS-affected women. It restores menstruation in all previously amenorrheic women. Furthermore, metformin decreases testosterone, free androgen index and dehydroepiandrosterone levels. Hence metformin can improve significantly hyperandrogenism and insulin resistance in PCOS patients and appears to be an efficacious mode of therapy.

Treating HIV Lipodystrophy

The use of antiretroviral combination therapy in HIV/AIDS has been associated with lipodystrophy and cardiovascular risk factors. Metformin improves visceral fat accumulation, fasting lipid profile and endothelial function and thus can be useful for treating HIV lipodystrophy.[18]

Fatty Liver

Nonalcoholic fatty liver disease (NAFLD) is an increasingly recognized health problem, which is characterized by inflammation and fibrosis. Disease presentation of NAFLD ranges from asymptomatic disease to cirrhosis with the complication of liver failure and hepatocellular carcinoma. In most cases; NAFLD is associated with insulin resistance, which is therefore the target of most current NAFLD treatment modalities. Metformin is one of the treatment strategies, besides weight loss and/or exercise, thiazolidinediones, lipid-lowering agents and antioxidants.[19]

Conclusion

A wide number of drugs are available today for effective treatment of diabetes and its complications. The effects beyond the conventional hypoglycemic effects of metformin offer advantages over other available oral hypoglycemic agents. Moreover, it is effective, well tolerated and can provide additional benefits in cardiovascular disorders and in other disease states. Discovering new uses for the old drug offers the advantage of providing time-tested drug for benefit of patients in a cost-effective manner, especially in developing countries with limited resources. Metformin represents one such drug which can be used in diverse areas of clinical practice.

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