

Renoprotective Effect of Metformin

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Type 2 diabetes mellitus is a serious health hazard all around the world and accounts for 90% to 95% of all diagnosed diabetes cases. It can be complicated with microvascular and macrovascular side effects such as coronary artery disease, stroke, retinopathy, and nephropathy. Although the majority of these complications have a multifactorial pathophysiology related to hyperglycemia, hypertension, dyslipidemia, and insulin resistance, the pathogenesis of vascular complications seems to be beyond hyperglycemia and glycated proteins. Thus, a drug with additional benefits other than glycemic control might be effective in reducing diabetic complications, especially the cardiovascular ones.

Metformin (dimethylbiguanide) is currently the most commonly prescribed oral antihyperglycemic agent in the world that primarily reduces blood glucose level and prevents insulin resistance. Recently, much attention has been paid to various advantages of metformin above other oral hypoglycemic drugs. Metformin is an effective oral antidiabetic drug, which increases liver and peripheral tissue sensitivity to insulin as well as reducing hepatic glucose production. It has multiple beneficial effects including reduction of atherogenic consequences of insulin resistance and antiplatelet aggregation effects. Metformin also reduces the rate of formation of advanced glycation end products. Numerous studies have shown favorable effects of metformin on lipid profile including modest improvement in the level of total cholesterol, low-density lipoprotein cholesterol and triglyceride and little or no change in high-density lipoprotein cholesterol levels.^{1,2} It is associated with redistribution of fat from viscera and reduced central obesity and body weight.³ Randomized trials have also shown improved

fibrinolysis and reduced risk of thrombogenesis following metformin use by declined plasma level or activity of plasminogen activator inhibitor 1 and reduced activity of clotting factors VII and XII.⁴

Metformin inhibits pro-inflammatory mediators (interleukin-1, interleukin-6, and interleukin-8) and nuclear factor κ B in human vascular smooth muscle cells.⁵ Additionally, metformin prevents the rise in oxidative stress and lipid peroxidation and reduces the level of reactive oxygen species (ROS) in human leukocytes by scavenging the free radicals or suppressing their intracellular production.⁶ Hyperglycemia induces oxidative stress by interfering with the activity of nicotinamide adenine dinucleotide phosphate oxidase, xanthine oxidase, and mitochondrial electron transport chain. Oxidative stress activates protein kinase C through the calcium-independent phospholipase A₂ in vascular tissues. Therefore, the activation of protein kinase C is related to both metabolic components and glucose-induced oxidative stress.⁷

The possible renoprotective effect of metformin has been subject to great attention recently. Morales and colleagues showed that metformin improved gentamicin-induced renal tubular injury in rats. This renoprotective effect might be possible because of the mechanism of gentamicin nephrotoxicity which includes the adverse role of ROS in a mitochondrial-dependent pathway.⁸ In another study, Amini and coworkers observed that metformin was able to prevent or attenuate the tubular damage by gentamicin or other nephrotoxic agents which act through the same mechanisms in Wistar rats.⁹ Gentamicin inhibits oxidative phosphorylation and reduces adenosine triphosphate levels in renal tubular cells. It increases ROS formation in cortical mitochondria and induces cell death. These mechanisms can partly be opposed by metformin.

Another possible mechanism for anti-oxidant effect of metformin is dependent on the mitochondrial permeability transition pore opening.⁹

In a preclinical study on Wistar rats, Rafieian-Kopaei and colleagues regarded the combination of metformin with garlic as another antioxidant to increase metformin's renoprotective efficacy.¹⁰ The results of their study suggest that metformin and garlic have curative and protective effects against gentamicin-induced nephrotoxicity. Likewise, Bruckbauer and colleagues showed synergistic effects of metformin, resveratrol and hydroxymethylbutyrate on insulin sensitivity. They found that the combination of hydroxymethylbutyrate and resveratrol with metformin has synergic effect on adenosine monophosphate-activated protein kinase-dependent pathways which lead to enhanced insulin sensitivity and therefore might reduce the therapeutic dose of metformin in diabetic patients. Additionally, this combination might also increase the antioxidant efficacy of metformin.¹¹

On the other hand, we know the clinical hallmarks of diabetic nephropathy include progressive albuminuria and decline in renal function. We also know that the loss of glomerular podocytes and podocytopenia are predictors of clinical nephropathy in the early phase of diabetic nephropathy. Glomerular capillaries include podocytes, glomerular endothelial cells, and glomerular basement membrane as their structural components. Podocytes have both true epithelial features of cell polarity and basement membrane and partial mesenchymal features. They consist of a cell body, major processes, secondary processes and foot processes. Thus, podocytes are important filtration barriers with cytobiologic and physiologic functions. Podocytes can be injured in human and experimental glomerular diseases leading to structural changes such as foot processes effacement and slit diaphragm disruption that are reversible. Therefore the injury to podocytes can lead to proteinuria and advanced proteinuria in patients with diabetic nephropathy has a poor prognosis.

Besides its anti-atherogenic, anti-inflammatory, and antioxidant effects, metformin reduces urine protein by preventing the injury to podocytes. Kim and colleagues suggested that renal podocyte injury is prevented by metformin in a rat model of type 2 diabetes mellitus.¹² In the current issue

of the *Iranian Journal of Kidney Diseases*, Nasri and colleagues offer a review article about metformin's renoprotective properties beyond its blood sugar regulatory effects. They show that metformin is not only beneficial for treating type 2 diabetes mellitus, but also has therapeutic effects in diabetic nephropathy and significantly decreases albuminuria in patients with type 2 diabetes mellitus. This might be related to metformin's role in activating adenosine monophosphate-activated kinase in tissues, decreasing intracellular ROS, and also preventing loss of podocytes in diabetic nephropathy.¹³

Considering the beneficial effects of metformin, we should certainly be cautious with its side effects. The glucose-lowering efficacy of metformin in type 2 diabetes mellitus is dose-related up to 2500 mg/d to 3000 mg/d. About 2000 mg/d may represent the optimal dose for most patients.¹⁴ The gastrointestinal side effects of metformin are usually mild and reversible with dose reduction. However, its major side effect, especially in high-risk patients such as patients with sepsis, kidney impairment, hypovolemia, and old age, is lactic acidosis. Therefore, metformin should be discontinued when estimated glomerular filtration rate declines to less than 30 ml/min and used with caution in patients with an estimated glomerular filtration rate of less than 60 mL/min.¹⁵

As previously mentioned, metformin is a safe, potent, and inexpensive first-line oral antiglycemic agent for treatment of type 2 diabetes mellitus in today's world. It has many advantages above other oral hypoglycemic drugs. It improves dyslipidemia and vascular endothelial function, reduces oxidative stress and apoptosis of endothelial cells, and has antithrombotic and anti-inflammatory effects, which decline the risk of cardiovascular mortality and morbidity. Recent research regarding the role of metformin in preventing diabetic nephropathy by tubular and podocyte mechanisms are mostly experimental. Therefore, clinical studies are considered necessary for the purpose of evaluating clinical end points such as changes in albuminuria and estimated glomerular filtration rate among diabetic patients.

Finally, there are several critical questions which need to be answered with large sample size clinical trials: Does metformin exert its renoprotective effect in patients with type 1 diabetes mellitus,

too? What is the optimal dose of metformin for renoprotection?

CONFLICT OF INTEREST

None declared.

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Urine Examination in the Era of Modern Diagnostics

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Urine examination, dipstick, and urine microscopy, the fundamental, common, and inexpensive diagnostic methods in nephrology have been replaced relatively by more sophisticated procedures in many nephrology units and have become one of the laboratory personnel tasks

and not nephrologists.¹ Tsai and colleagues, in their study of acute kidney failure, showed the increased chance of correct diagnosis from 19.2% to 69.3% when urinalysis report was done by a nephrologist.² Fogazzi and colleagues compared in their well-designed study the features of urine