KIDNEY DISEASES IJKD

Bright Renoprotective Properties of Metformin
Beyond Blood Glucose Regulatory Effects

Hamid Nasri,[1] Azar Baradaran,[2] Mohammad Reza Ardalan,[3] Saeed Mardani,[4] Ali Momeni,[4] Mahmoud Rafieian-Kopaei[4]

[1]Department of Nephrology, Division of Nephropathology, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of Clinical Pathology, Isfahan University of Medical Sciences, Isfahan, Iran
[3]Chronic Kidney Disease Research Center, Tabriz University of Medical Sciences. Tabriz, Iran
[4]Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran

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Metformin, a biguanide drug, is widely prescribed to treat high blood glucose in individuals with type 2 diabetes mellitus. Type 2 diabetes mellitus is a troubling chronic disease and diabetic nephropathy is one of the most important complications of diabetes mellitus. Recent studies suggest that metformin, in addition to its efficacy in treating type 2 diabetes, may also have therapeutic efficacy in other conditions, including diabetic nephropathy or ameliorative property against tubular cell injury. Moreover, metformin significantly decreases albuminuria in patients with type 2 diabetes mellitus. However, the exact mechanisms beyond the effect of metformin on blood glucose are still unknown. Recent studies suggest that the therapeutic effect of metformin is mediated by its action on adenosine monophosphate-activated protein kinase in tissues. Various investigations show that metformin decreases intracellular reactive oxygen species. Metformin protects against tubular injury by restoring the biochemical alterations and regulation of oxidative stress on renal tubules. It also protects podocytes in nephropathy of diabetes. These findings can more strongly potentiate the clinical use of metformin in the prevention of nephropathy of diabetes. In this regard, to better understand the metformin nephroprotective properties, more experimental rat models and clinical studies are needed.

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Review

INTRODUCTION

Metformin, an oral antidiabetic drug in the biguanide class is a widely prescribed drug to treat high blood glucose in individuals with type 2 diabetes mellitus (DM).[1,2] Despite clinical introduction in the 1950s, the exact mechanism action of metformin is not yet fully understood. Indeed, considerable research has been made from many years ago to better discover the molecular and cellular mechanisms of action of metformin.[2,3] The antihyperglycemic properties of metformin are mainly attributed to the suppression of liver glucose production and increase in peripheral tissue insulin sensitivity.[4] This drug improves insulin sensitivity without decreasing the glucose concentration below normal values.[4] Metformin has 90% to 100% renal excretion as unchanged drug, and its clearance is reduced in kidney dysfunction. Metformin plasma half-life is 1.5 to 4.9 hours in healthy persons.[5] Metformin has high water solubility, negligible protein binding in serum, and a large volume of distribution, because it diffuses freely into the intracellular compartment and binds to microsomes.[4,5] By a mild and transient inhibition of respiratory-chain complex 1 in the mitochondria, metformin can decrease liver glucose production.[6-9] Moreover, the decrease in hepatic energy status, leads activation of adenosine

monophosphate-activated protein kinase (AMPK), which may explain the mechanism of metformin action on liver gluconeogenic process.[10]

In addition to its effect on blood glucose, metformin was also reported to have beneficial effects on microvascular and macrovascular complications associated with type 2 DM.[11] Furthermore, metformin is beneficial in gestational DM, for the prevention in prediabetic persons.[12-14] In addition, by increasing sensitization to insulin and resultant reduction in insulin resistance, reduction in plasma fasting insulin level was also found with metformin, too. The improvement of sensitivity to insulin by metformin could be attributed to its positive effects on insulin receptor expression and tyrosine kinase activity.[12-15] Recent findings have established that metformin possesses antioxidant properties, too.[11,16,17] Reduction of apoptosis, induced by oxidative stress, in endothelial cells and prevention of vascular dysfunction were also found with metformin treatment. In this review, the renal tubular protective efficacy of metformin and its protective efficiency in diabetic kidney disease are discussed.

MECHANISM OF ACTION

As mentioned above, the activation of AMPK was intimately associated with the pleiotropic actions of metformin,[18] and this enzyme regulates cellular and organ metabolism.[17-20] The AMPK is a phylogenetically conserved serine/threonine protein kinase envisaged as a fuel gauge monitoring systemic and cellular energy condition,[18,19] and plays an important role in protecting cellular functions under energy-restricted conditions.[20] Ample evidence attests that AMPK activation by metformin is secondary to its effect on the mitochondria as the primary target of this agent.[19,20] Recent findings mentioned to the direct or mediated mitochondrial effect of metformin.[21] Indeed, there is evidence that when it is used alone, the beneficial effect of metformin may be due to its mild inhibition of the mitochondrial respiratory chain (mainly of complex I).[21-23] Various findings imply that metformin has ameliorative properties against toxic effects to the renal tubules.[22-26] Among functions of mitochondria, their role in cell death and life decisions has gained special importance.[25,26] While the crucial role of mitochondria in cell death is of significance, protecting mitochondria has become a prosurvival cell strategy.[24-26] In this regard, the role of mitochondria in programmed cell death is associated with the release of apoptotic signaling molecules.[11,25-31] Moreover, reactive oxygen species (ROS) production by mitochondria may also lead significantly to any cell degradation process.[24,27-29] The mechanism of mitochondrial ROS production in cells is not fully understood, because most of studies revealing ROS production were made in model systems.[28,30] It was found that mitochondria represents one of the major cellular sources of ROS generation,[28-30] and a great number of tissue pathologies, both inherited and acquired, were found to be associated with oxidative stress.[30,31] These findings showed the critical role of mitochondria in these conditions.[31,32] Previously, Morales and colleagues observed that gentamicin-induced renal tubular damage is attenuated by metformin.[33] Reactive oxygen species play a key role in the toxicity of gentamicin, resulting in acute kidney failure,[34-36] and gentamicin is a mitochondrial toxin that can imply its toxic effects when excreted by the kidney.[37-39] Mitochondrial toxicity can also be mediated by reactive oxygen species.[24,32] Reactive oxygen species are normally produced at low levels by mitochondria; however, under pathological conditions the intracellular and intra mitochondrial ROS content may be increased.[22-24] Indeed, in certain conditions, intracellular ROS content can reach a toxic level, which results in oxidative damage to the mitochondria, causing cell death and malfunctioning of the organ.[22-24]

To test the potential properties of metformin to protect the kidney from gentamicin-induced acute kidney failure and also finding out that whether postpone treatment with metformin in acute kidney failure exerts similar benefits on gentamicin nephrotoxicity in rats, we conducted a study on male Wistar rats.[40] We found out that metformin prevented and also ameliorated gentamicin-induced acute kidney failure, and hence, it might be beneficial in patients under treatment with this drug.[40] Recently, we also tested the efficacy of co-administration of garlic extract and metformin for prevention of gentamicin-renal tubular damage in 70 male Wistar rats. The result of this study demonstrates that metformin and garlic juice or their combination has both curative and protective effects against gentamicin nephrotoxicity.[41] Accordingly, Taheri and coworkers recently conducted a study

on the effects of metformin on renal function and structure after unilateral ischemia-reperfusion in rats. They found that metformin provided some renal protection against ischemia and reperfusion induced damage to the rats' kidney.[42] Likewise, they also concluded that metformin with activation of AMPK and endothelial nitric oxide synthase have tissue protective effects.[40] Thus, these data lend further evidence for the attribution of metformin in its renoprotective property in addition to its well-known hypoglycemic action.

METFORMIN AND NEPHROPATHY

Diabetes mellitus is constituted of a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion or action,[43-45] and diabetes is nephropathy is one of the most important complications of DM.[46] Recently, much attention has also been directed towards the possible protective ameliorative role of metformin in diabetic kidney disease, too. Hyperglycemia amplifies oxidative stress and generation of ROS, which have a crucial role in the pathogenesis of diabetic nephropathy.[47,48] In the study conducted by Alhaider and colleagues the effect of metformin on the biochemical changes associated with hyperglycemia was investigated in rat kidney tissues.[49] In addition, they also assessed energy nucleotides (adenosine monophosphate and adenosine triphosphate), and acetyl-CoA in the renal homogenates and mitochondria and also pro-inflammatory mediators. They found that treatment of normoglycemic rats with metformin caused significant increase in adenosine triphosphate and acetyl-CoA, contents in kidney homogenates and mitochondria along with profound decrease in adenosine monophosphate level. Also, treatment of nephropathy of DM in rats with metformin normalized all biochemical changes and the energy status in kidney tissues. At the transcriptional levels, metformin treatment caused significant restoration in diabetic nephropathy-induced oxidative stress mRNA levels.[49]

Evidence suggests that ROS overproduction may be the key starting event that results to the long-term development of complications of diabetes.[50-52] However, the specific mechanisms that link hyperglycemia with oxidative stress and diabetic nephropathy are poorly found.[49,51,53] In general, nucleic acids can affected by oxidative stress and generate various modified bases in DNA. When DNA is damaged, affected cells start a response, such as DNA repair, cell cycle delay or apoptosis induction. The ROS generation by oxidative stress causes cell death.[54-56] Apoptosis has been implicated in the pathogenesis of nephropathy of diabetes and reactive oxygen species is an inducer of apoptosis in various cell types including podocytes.[54-58] More recently, Kim and colleagues conducted a study using metformin for diabetic rats. They observed restoration of podocytes by metformin treatment in diabetic rats. They suggested that diabetes-induced podocyte loss in nephropathy of diabetes could be attenuated by metformin, by the repression of oxidative injury.[59] They also showed that the density of podocytes decreases in diabetic rats in association with increased albumin excretion. Podocyte apoptosis has been detected to associate with increasing albuminuria. Moreover, there was evidence for the role of intracellular ROS as potent inducers of podocyte apoptosis, too.[59] Therefore, metformin acts as an activator of AMPK, a major cellular regulator of glucose and lipid metabolism, and as an inhibitor of complex I of the respiratory chain in the mitochondria. Kim and colleagues found that the phosphorylation of AMPK was reduced in the kidney of diabetic rats, and metformin could restore its alteration. Therefore, metformin may exert some of its effects by improvement of renal oxidative stress. They suggested a potential clinical use of metformin in the prevention of diabetic kidney disease by inhibition of advanced glycation end products and free radical defense system improving.[59] These findings are in agreement with the study conducted by Liu and colleagues. They pointed the beneficial antioxidant properties of metformin in diabetic rats too.[60]

It is well known that the injury of podocyte leads to the occurrence of proteinuria; therefore, the loss of glomerular podocytes precedes and predicts the onset of nephropathy and may be an early pathological manifestation of diabetic nephropathy. Metformin significantly decreased albuminuria in patients with type 2 DM.[61] Previous studies have also shown the beneficial effects of metformin on reduction of macrovascular morbidity and mortality, suggesting that it implies antiatherogenic, antioxidant, and anti-inflammatory effects.[59,61-63] Moreover, metformin significantly

decreased albuminuria in patients with type 2 DM.[59,61-63] The benefits of metformin using with its cardiovascular and metabolic parameters benefits suggest its clinical use in treating chronic kidney disease, too.[1,7] The glomeruli have been at the focus of attention as the primary site of damage in diabetic kidney disease; however, it is also well known that tubulointerstitial changes are a prominent constituent of the disease, especially in patients with type 2 DM.[64-66] The level of albuminuria and diabetic kidney disease progression best correlate with tubular degeneration and interstitial fibrosis.[64-66] In fact urinary biomarker data in human beings provide the view that proximal tubule damage contributes in a primary way, rather than in a secondary fashion, to the development of early diabetic kidney disease.[66,67] Indeed, in the process of diabetic nephropathy, capillary rarefaction leads to local ischemia with further injury to the tubules, more profibrogenic mediators, matrix protein deposition, fibrosis, and aggravating the glomerulosclerosis.[64-68] Hence, in diabetic kidney disease, the tubules show alterations that are usually associated with glomerular alterations, tubular cell degeneration, tubular apoptosis, and tubular atrophy.[64-68] Therefore, it is reasonable to imply that metformin has 2 different roles: first, renal tubular cell protection, by acting as an effective antioxidant, and second, its ameliorative effect on diabetic kidney disease. However, diabetic patients may benefit from both of these two distinct properties, as well as its blood glucose regulatory effects.

CONCLUSIONS

Type 2 DM is a troubling chronic disease. Regarding the huge number of new cases diagnosed annually in the world, and diabetic nephropathy is one of the most important complications of DM. Recent studies suggest that metformin, in addition to its efficacy in treating type 2 DM, may also have therapeutic potential in other conditions including diabetic nephropathy. It may also be beneficial as an ameliorative agent against tubular cell injury. Moreover, metformin significantly decreases the urine albumin excretion rate in patients with type 2 DM. However, the exact mechanisms beyond the effect of metformin are still are unknown. Recent studies suggest that therapeutic effect of metformin is mediated by its action on AMPK in tissues. Various investigations show that metformin decreases intracellular ROS. Metformin protects tubular injury by restoring the biochemical alterations and regulation of oxidative stress on renal tubules. Metformin also protects podocytes in diabetic nephropathy.

These findings can potentiate the clinical use of metformin in the prevention of nephropathy of DM. In this regard, to better understand the metformin nephroprotective properties, more preclinical and clinical studies are suggested.

CONFLICT OF INTEREST

None declared.

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Correspondence to:
Hamid Nasri, MD
Department of Nephrology, Division of Nephropathology, Nour Medical, Educational & Therapeutic Center, Isfahan University of Medical Sciences, Isfahan, Iran
Tel: +98 311 6692609
Fax: +98 311 223 5043
E-mail: hamidnasri@med.mui.ac.ir

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