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Metformin and prevention of diabetic kidney disease

Amin Hasanvad*

Department of Pharmacology and Toxicology, Faculty of Pharmacy, Lorestan University of Medical Sciences, Khorramabad, Iran

***Correspondence to**
Amin Hasanvand, PhD;
Email: dr.hasanvand@yahoo.com

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Core tip

Metformin is the class of oral glucose-lowering drugs widely used for the prevention or treatment of type 2 diabetes. AMP-activated protein kinase (AMPK) via metformin, a cellular energy regulator, can be used to balance hemostasis. Many studies showed that hyperglycemia significantly inhibited the AMPK and increased activation of mTOR pathway, and also, it was induced hypertrophy and renal injury leading to diabetic nephropathy. It is clear that metformin attenuates oxidative stress through via AMPK signaling pathways contributing to its nephroprotective effects in diabetic nephropathy (diabetic kidney disease).

Metformin is the class of oral glucose-lowering drugs widely used for the prevention or treatment of diabetes mellitus type 2 (T2D) (1). Metformin is a stimulation of 5' adenosine monophosphate-activated protein kinase (AMPK) and thus induces up-regulated fatty acid oxidation and glucose uptake in peripheral tissues, and also, it causes a decrease in lipogenic genes and hepatic glucose production (2). Additionally, metformin has also been shown to have beneficial effects on urine albumin excretion rate in patients with type 2 diabetes (3). Reductions in AMPK signaling activation is also confirmed in kidney tubular cells exposed to elevated glucose milieu in patients with type 2 diabetes, and the induced AMPK activation via metformin treatment has been shown to significant decreases hyperglycemia-induced renal injury (4). Studies have shown that activation of AMPK by metformin reduces blood glucose levels and is normalized to expression GLUT1 in the diabetic model in the rodent (5). Many studies showed that hyperglycemia significantly inhibited the AMPK and increased activation of mTOR pathway, and also, it was induced hypertrophy and renal injury leading to diabetic nephropathy (diabetic kidney disease). Metformin is also known to have antioxidative effects via suppression of NADPH oxidase in renal podocytes (6). It is proven that the antioxidant effect of metformin is dependent on the AMPK activation. Activation of AMPK via metformin is a potent way to prevent podocyte apoptosis in a rodent model of type 2 diabetes (7). Additionally, in a study by Alhaider et al, administration of metformin in experimental models of type 1 diabetes has been also shown to attenuated oxidative stress mRNA levels, particularly GSTα, NQO1, and CAT genes, in streptozotocin-induced diabetic kidney disease in rats (8). Advanced glycation end products (AGEs) and its receptor RAGE (receptor for advanced glycation end-products) play the main role in the progress of renal injury in diabetic disease. Metformin attenuates levels of AGEs by down-regulating the expression of RAGE and it inhibits the generation of hyperglycemia-induced reactive oxygen species (9). One study in rats demonstrated that metformin significantly decreases the gentamicin-induced mitochondrial oxidative stress, lipid peroxidation and intensification in antioxidants levels (10). Thus, it is clear that metformin attenuates oxidative stress through via AMPK signaling pathways contributing to its nephroprotective effects in diabetic kidney disease. Metformin can be diminishing sterol regulatory element-binding protein-1, fatty acid synthase and acetyl CoA carboxylase expression in diabetic nephropathy and it causes a nephroprotective effect in renal (11). The

decrease of kidney lipotoxicity by metformin could thus be a novel plan for the suppression of diabetic kidney disease. Interestingly, the other effects of metformin are attenuated of cystic formation and growth in the ADPKD (12).

Authors' contribution

AH is the single author of the manuscript.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Conflicts of interest

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