

# Metformin and kidney protection; a letter to editor on recent findings

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**Received:** 15 August 2018

**Accepted:** 9 February 2019

**ePublished:** 14 April 2019

**Keywords:** Metformin, Antioxidative, Anti-inflammatory

## Core tip

The mechanism of metformin includes the enhancement of skeletal muscles and adipocytes glucose uptake, and inhibiting the production of glucose in liver. AMP-activated protein kinase (AMPK) via metformin, a cellular energy regulator, can be used to balance hemostasis. Treatment with metformin in glomerular mesangial cells (MCs) in a diabetic situation has resulted in the significant increase of superoxide dismutase (SOD) and malondialdehyde (MDA), monocyte chemoattractant protein-1 (MCP-1), p38 mitogen-activated protein kinase (p38MAPK) expression, the expression of nuclear factor- $\kappa$ B (NF- $\kappa$ B), intracellular p22phox mRNA and protein level, intercellular adhesion molecule-1 (ICAM-1), proinflammatory cytokines, transforming growth factor-beta 1 (TGF- $\beta$ 1) and ROS production suppression and lipid peroxidation. Metformin also has a reno-protective mechanism, i.e., restoring mitochondrial function integrity.

**Citation:** C. Koushki S, Mohammadrezaei Khorramabadi R, Amanolahi Baharvand P, Hasanvand A. Metformin and kidney protection; a letter to editor on recent findings. J Prev Epidemiol. 2019;4(1):e07.



## Introduction

Metformin (dimethylbiguanide) is an oral anti-hyperglycemic drug that has been considered as an effective therapy for type 2 diabetes mellitus. The mechanism of metformin includes the enhancement of skeletal muscles and adipocytes glucose uptake, and inhibiting the production of glucose in the liver. It can also raise insulin sensitivity that in turn leads to the decrease of insulin dose requirement and weight loss (1,2).

## Metformin and its mechanism

The molecular mechanism of metformin for balancing the level of glucose is not precisely clear, but previous studies have shown the effect of AMPK signaling pathway activation. Metformin has several anti-atherosclerotic and anti-inflammatory beneficial effects on various types of cells such as endothelial and smooth muscle cells. proinflammatory responses, including lipopolysaccharide (LPS) or oxidized LDL in inflammatory cells such as monocyte and macrophage, are also attenuated by metformin (3). It has several antioxidative and anti-inflammatory effects against different diseases including cerebral ischemia (4), stroke in rat model (5), tobacco smoking (TS) or cigarette smoking

(CS), brain injury(6), spinal cord injury (7), inflammatory bowel disease (IBD) (8,9), myocardial injury (10), acute kidney injury (11), and acute lung injury of rat model (12). Previous studies have indicated that metformin could prevent various types of renal diseases ranging from acute kidney injury (AKI) (13). Although some studies have reported the complications of metformin in the kidney, which can be considered as overestimated reports in comparison with its beneficial effects (14), anti-oxidative and anti-inflammatory functions of metformin protects renal cells by ameliorating serum, blood and urea nitrogen. It can decrease the level of serum creatinine and creatinine clearance. Metformin not only reduces the amount of urinary albumin excretion but also decreases fasting blood glucose. Moreover, metformin ameliorates the oxidative/nitro-oxidative stress level via decreasing the level of lipid peroxidation assessed malondialdehyde (MDA) and increasing superoxide dismutase (SOD). Metformin also improves lipid profile via reducing total body cholesterol (TG), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and increasing high-density lipoprotein cholesterol (HDL-C) (15). AMP-activated protein kinase (AMPK), a cellular energy

regulator, can be used to balance hemostasis. Chronic kidney disease (CKD) is a result of increasing the level of renal cellular apoptosis and epithelial-to-mesenchymal transition (EMT) that is caused by deficiency in AMPK activation and its intracellular signaling pathways, autophagic signaling, mammalian target of rapamycin (mTOR) sustained activation and endoplasmic reticulum (ER) stress. Metformin as a pharmacological AMPK activator could prevent and treat chronic kidney disease (16). In hyperglycemic or diabetic conditions, the decrease of AMPK and activation of mTOR signaling axis and reactive oxygen generation leads to renal cells, podocytes (podocytes and podocytopenia are diagnostic predicting factors in diabetic nephropathy) (17) and apoptosis. It also damages renal functions including structural integrity and glomerular filtration. Metformin improves diabetic nephropathy by reversing all of the above mentioned cases (18). It can suppress albuminuria, and balance renal tubules oxidative stress level as well as reactive oxygen species (ROS) in diabetic nephropathy (19). Metformin decreased inflammation via inhibiting interleukin-1, interleukin-6, TNF-alpha, and elevated the anti-oxidative response, and also attenuated tubular damage (20). Treatment with metformin in glomerular mesangial cells (MCs) in a diabetic situation has resulted in the significant increase of SOD and MDA, monocyte chemoattractant protein-1 (MCP-1), p38 mitogen-activated protein kinase (p38MAPK) expression, the expression of nuclear factor- $\kappa$ B (NF- $\kappa$ B), intracellular p22phox mRNA and protein level, intercellular adhesion molecule-1 (ICAM-1), transforming growth factor-beta 1 (TGF- $\beta$ 1) and ROS production suppression and lipid peroxidation (21,22). Metformin also has a reno-protective mechanism, i.e., restoring mitochondrial function integrity (17). In an ischemia-reperfusion of kidney, AMPK activation and autophagy are not enough to reduce cellular damage and maintain cellular homeostasis. Moreover, the expressions of stress-responsive and apoptotic marker level increase. Metformin could induce AMPK activation and improve cellular homeostasis (23). It has a protective effect in diabetic nephropathy (DN) caused by streptozotocin (STZ). Metformin can improve renal function via decreasing the level of TNF- $\alpha$ , TGF- $\beta$ , MPO and nitrite production (24). Metformin has a protective effect on autosomal dominant polycystic kidney disease (ADPKD) via activating AMPK signaling pathway. Metformin also reduces gentamicin-induced nephropathy via ameliorating oxidative stress, maintaining the integrity of mitochondrial function and decreasing the level of serum BUN and serum creatinine (25).

## Conclusion

To conclude, metformin was also effective in decreasing several measures of renal injury. Metformin thus suggests an effective handling choice for the management of patients with renal injury.

## Conflicts of interest

The authors declare that there are no competing interests.

## Authors' contribution

SK, RMK, PAB and AH were involved in drafting of the manuscript and revising it critically for important intellectual content.

## Acknowledgments

The authors wish to thank the Deputy for Research and the School of Pharmacy of Lorestan University of Medical Sciences.

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