A short look to the nephroprotective impacts of metformin

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ARTICLE INFO

Article Type: Editorial

Article History:
Received: 13 December 2015
Accepted: 14 January 2016
ePublished: 24 January 2016

Core tip: Recently various investigation have detected that treatment with metformin attenuates kidney, liver and heart fibrosis. These studies were shown that metformin is capable to inhibit TGF-β1-induced epithelial-to-mesenchymal transition which plays a main role in inhibiting malignancy extension and organ fibrosis.

Please cite this paper as: Baradaran A. A short look to the nephroprotective impacts of metformin. Toxicol Persa. 2016;1(1):e01.

Keywords: Metformin, Kidney, Epithelial-to-mesenchymal transition, Type-2 diabetes, Transforming growth factor-β1.

Introduction

Metformin was basically originated from the French lilac Galega officinalis, and now is a widely recommended biguanide administered as a first-line antidiabetic drug. Metformin is safe and efficient in the treatment of diabetes and usually does not induce hypoglycemia (1). Regardless of its known blood glucose regulating properties, metformin has been shown to produce favorable effects as a nephroprotective agent and has ameliorative effects in diabetic kidney disease (1, 2). In this paper we will review the recent data on pleiotropic impact of metformin in experimental and clinical investigations.

Materials and Methods

For this paper, we used a diversity of sources by searching through PubMed/Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following key words and or their equivalents; metformin, kidney, epithelial-to-mesenchymal transition, type-2 diabetes and transforming growth factor-β1.

Administration of metformin in clinical medicine

Metformin has been extensively administered for the treatment of type-2 diabetes without inducing overt hypoglycemia. It has good safety profile, practically no risk of hypoglycemia. Moreover, metformin, has lipid-lowering property, efficiency in preventing micro- and macrovascular complications, and also body weight reduction effect. The probable mechanisms comprise reducing insulin resistance, decreasing hypercoagulation, favorable influence on vascular smooth muscle, improving endothelial function, improving lipid metabolism, and also improving intracellular calcium handling within cardiomyocytes (1-3). While, metformin is a mostly used first-line antidiabetic medication, however, it has been detected to protect against various diseases in addition to diabetes, including polycystic ovary syndrome, cancer and cardiovascular diseases. The United Kingdom Prospective Diabetes Study (UKPDS) established that metformin had heart and vessels protective impact beyond its anti-hyperglycemic influence (2, 3). In fact, chronic renal failure and diabetes mellitus especially type 2 of diabetes mellitus (T2DM) signifies a global public health problem. The incidence of these illnesses is progressively growing into epidemic proportions.

Renoprotective impact of metformin

Previously, Morales et al (4) showed prevention of experimental gentamicin-induced renal injury, which was interpreted to mediate through a mitochondria-dependent pathway. They also detected, renal protection of metformin by improving histological injury six days after gentamicin administration. Morales et al noticed that therapy with gentamicin depleted respiratory components (cytochrome c, NADH), possibly due to the opening of mitochondrial transition pores. They concluded that, renal damages, partially mediated by an increase in reactive oxygen species from the electron transfer chain and this process were significantly subsided by metformin. They suggested that pleiotropic impact of metformin can diminish gentamicin renal toxicity and is able to improve mitochondrial homeostasis (4). In an experimental investigation we also showed the amelioration of renal injury by metformin in rates treated by gentamicin. In this preclinical investigation, a significant amelioration of

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renal function test and histological alterations induced by gentamicin by oral metformin. We, furthermore, detected post-treatment with metformin as like the co-treatment with metformin could prevent the rise of serum blood urea nitrogen and creatinine induced by intraperitoneal gentamicin and also lessens the histological injury score. In this study, we concluded that, metformin may prevent or improve gentamicin induced acute kidney injury, and thus it might be useful in prevention in patients may be at exposure to nephrotoxic substances (2-5).

Mechanisms of pleiotropic properties of metformin

Various studies have detected that, transforming growth factor-β1 (TGF-β1) is implicated in the progression of various illnesses, consisting cardiovascular, renal and immunological diseases. TGF-β1 is associated with fibrosis, inflammation and epithelial-to-mesenchymal transition (EMT) which are main pathological alterations in these diseases (1-3). It is largely recognized that metformin acts through the activation of AMP-activated protein kinase (AMPK) and suppression of mitochondrial respiratory-chain complex 1. Furthermore, metformin suppresses TGF-β1 induced collagen synthesis independent of AMPK activation. It was shown that, metformin antagonizes TGF-β1 signaling through a direct binding of metformin to TGF-β1 a process that is independent of AMPK activation pathway (4-6).

Recently various investigations have detected that treatment with metformin attenuates kidney, liver and heart fibrosis.

Conclusion

These studies were shown that metformin is capable to inhibit TGF-β1-induced epithelial-to-mesenchymal transition which plays a main role in inhibiting malignancy extension and organ fibrosis, while various clinical trials have proposed a decreased in cancer risk and also an improved prognosis in cancer patients through metformin therapy. These results confirm the hypothesis that metformin applies its protective property against organ fibrosis and malignant tumor extension through blocking TGF-β1 (6-8).

Author’s contribution

AB was the single author of the manuscript.

Conflicts of interest

The author declared no competing interests.

Ethical considerations

The authors of this manuscript declare that they all have followed the ethical requirements for this communication. Also, Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Funding/Support

None.

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