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A nephrology viewpoint on renoprotective properties of metformin

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Abstract

Globally diabetes is a major cause of kidney failure. Metformin is non-nephrotoxic and one of the first choice hypoglycemic agents in treatment of diabetes. We reviewed the effect of metformin in diabetic kidney disease (DKD). Directory of open access journals (DOAJ), Google Scholar, PubMed, EBSCO, and Web of Science with keywords relevant to; chronic kidney disease, diabetes mellitus, metformin, diabetic nephropathy, have been searched. Diabetes causes expression of extracellular matrix mediators and secretory factors that eventually lead to morphological changes in mesangial, interestitium and glomerular cells. The biguanide, metformin is derived from French lilac (*Galega officinalis*). Metformin is a commonly prescribed drug for type II diabetes around the world due to its safety record and reduction of micro-vascular and cardiovascular events. It appears that metformin has multiple roles in protecting kidney in diabetic patients by tubular cell protection, improving hypertension, albuminuria and restoring the glomerular podocytes. It may be justified to use metformin for nephron-protection in early stage of DKD.

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Introduction

Globally diabetes is a major cause of kidney failure. The International Diabetes Federation reported around 5 million deaths related to diabetes in 2014. It has been estimated that the number of diabetic population will increase to 592 million by 2035 and more than 75% of these population reside in developing countries. Metformin (miraculous tincture of *G. officinalis*) is one of the first choice medications in the treatment of diabetes.

For this review, 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; chronic kidney disease, diabetes mellitus, metformin and diabetic nephropathy

Core tip

Diabetic kidney disease is becoming a major public health problem due to high morbidity, mortality and cost. It has been shown that metformin reduces macrovascular complications and mortality in individuals with type 2 diabetes mellitus. It may be justified to use metformin for nephron-protection in patients with early stage of diabetic kidney disease (DKD). Further clinical investigation on this subject is needed.

Galega officinalis and metformin

In the recent decades, metformin has been one of the interesting research subjects due to its positive impacts on the treatment of type 2 diabetes. It is the only approved anti-diabetic drug that was developed from an herbal source with a long history of use for diabetes. The biguanide, metformin is derived from French lilac (*Galega officinalis*). *G. officinalis* is a good resource of biological active compounds like guanidine (1918) and related molecules. Side effects and toxicity of guanidine are limited in its medical use. Furthermore Tanret extracted galegine and isoamylene guanidine in 1920 as a compound that had a less side effect profile than guanidine. Initial studies showed that galegine reduced weight gain, blood glucose and food intake in mice, suggesting that, part of the effect of *G. officinalis* on body mass

was mediated through galegine. The mechanism of this action is not clearly understood, but involves loss of body fat. The exact structure of galegine was confirmed as isoamylene guanidine in 1923. Subsequently, two synthetic diguanides, namely decamethylene diguanide (synthalin A) and dodecamethylene diguanide (synthalin B), were used clinically in treatment of diabetes. Those medications were effective and tolerated better, but their association with lactic acidosis led to discontinuation of these drugs in most countries by the end of the 1970s. Searches for an anti-hyperglycemic agent without causing weight gain or hypoglycemia lead to the discovery of another biguanide named metformin (1,2).

Diabetic kidney disease

The prevalence of type II diabetes has increased at an alarming rate over the past several years. Chronic kidney failure is becoming a major public health problem due to high morbidity, mortality and cost. The leading risk factor for chronic kidney disease (CKD) is diabetes associated with various complications. Chronic renal failure resulting from diabetes has been termed diabetic kidney disease (DKD) (3). The complications of type II diabetes mellitus, especially end-stage renal disease, accounts for the largest portion of the cost of the disease. DKD is a potentially fatal diabetic vascular complication defined by slowly increasing proteinuria and a gradual decrease in kidney function. The pathogenesis of DKD has been intensely studied for decades and several mechanisms have been proposed. The effect of high glucose on glomerular hyperfiltration, activation of the protein kinase C, polyol pathway, renin–angiotensin system, reactive oxygen species, increase of advanced glycation end-product (AGE) and lastly autonomic nervous system imbalance are some of the main culprit in DKD (4,5). These abnormalities result in several cellular reactions; expression of extracellular matrix mediators and secretory factors that eventually leads to morphological changes in mesangial, interestitium and glomerular cells. DKD is distinguished morphologically by glomerular hypertrophy, thickening of the glomerular basement membrane, expansion of the mesangial matrix, interstitial fibrosis with tubular atrophy, and finally glomerulosclerosis. Progressive accumulation of the mesangial matrix obliterates the glomerular capillary tufts and results in kidney failure (6).

Oxidative stress in diabetic kidney disease

Oxidative stress in diabetic subjects is related to overproduction of reactive oxygen species and decreased efficacy of antioxidant mechanisms. Diabetes-associated metabolic disorders disturb the activities of various enzymes in the mitochondrial respiratory chain complex. Importantly, oxidative stress is closely related to mitochondrial dysfunction. Equally important, nitrosative stress and oxidative stress mediate the harmful effects of diabetes on kidney function. Micro-vascular changes and acceleration of collagen IV accumulation in mesangium may be induced by high glucose and induction of reactive oxygen radicals. The main targets of current standard therapies of DKD are strict control of blood pressure, blood sugar and a blockade of the renin-angiotensin system (7). Regardless of these modalities, DKD is still found to be progressive with high morbidities (8).

Administration of metformin in diabetic patients

Metformin is a commonly prescribed drug for type II diabetes around the world. It belongs to the biguanide class and has priority in the treatment of type II diabetes due to its safety record and reduction of micro-vascular and cardiovascular events. Several studies have shown the safety of using metformin in CKD II (9,10). Metformin reduces diabetes-related mortality and morbidity in comparison with sulphonylurea or insulin in type II diabetic patients (11). Enhanced thrombolysis, reduced plasma concentrations of fibrinolysis inhibitor and non-enzymatic glycation improvement of dyslipidemia are possible mechanisms that have been proposed (12). The effects of metformin on lipid profile and blood pressure have been tested and observed in animal models, yet these effects on human models are still debated (4,13). In this review article, we aimed to review the effect of metformin in DKD.

Preclinical points of view

Metformin improves the insulin resistance primarily in adipose tissues, muscle and the liver by diminution in the rate of glycogenolysis and gluconeogenesis. Other beneficial effects of metformin consist of weight loss, lipid-lowering properties, attenuation of endothelial dysfunction, subclinical inflammation and antineoplastic effect (14-17). Metformin is a non-nephrotoxic drug which was initially chosen as the safest hypoglycemic agent in CKD, but its usage has been limited due to perceived risk of lactic acidosis in this population (11). Metformin reaches to its maximum plasma concentration in one to three hours after ingestion and does not bind to plasma proteins. Its volume of distribution is up to 1000 L, after one 1000 mg oral single dose. Metformin is eliminated unchanged through glomerular filtration and tubular secretion; and is transported mainly through organic cation transporters (OCTs) particularly type 1 and 2 and multidrug and toxin extrusion proteins (MATEs), namely MATE1, which is highly expressed in the renal tissue, and MATE2. Metformin inhibits gluconeogenesis in the liver and stimulates glucose uptake in fat and muscle tissues. The therapeutic action of metformin is mediated through its action on AMP-activated kinase (AMPK) that switches the cells from anabolic to catabolic state and restoring energy balance (18,19). Metformin considerably reduces the urine albumin excretion rate in patients with type II diabetes (20). Metformin suppresses the diabetes-induced loss of podocytes by suppression of oxidative stress in the rat model (21). Several studies have been proposed that metformin decrease NAD(P)H oxidase activity and reactive oxide species (ROS) generation and activate AMP-activated kinase in cultured podocytes, hence suppressing the production of pro-inflammatory cytokines (12,22,23). Metformin also enhanc-

es production of nitric oxide (NO) and endothelial nitric oxide synthase (eNOS) in endothelial cells, which helps in decelerating the atherosclerosis process (19).

Recent studies have been suggested that the NO deficiency and elevated asymmetric dimethylarginine levels are correlated with the development of high blood pressure. Metformin is a structural analog of asymmetric dimethylarginine. It has been shown that metformin prevents the development of high blood pressure in spontaneously hypertensive rats by restoration of asymmetric dimethylarginine-NO balance (24,25). Prescribing metformin as an antihypertensive agent in patients with DKD has not become an established treatment.

In recent years much attention directed toward renal tubular cell protection of metformin. In the past, the improvement of mitochondrial homeostasis by metformin through diminishing apoptosis and cell death has been reported (26). It has been shown in the rat model that metformin is able to improve gentamicin induced acute kidney injury. It has been also established that co-administration of metformin and garlic extract are able to prevent gentamicin nephrotoxicity in rats (27). Janjua et al confirmed renoprotective effects of metformin against gentamicin induced renal toxicity in rabbits (20). Zhang et al (28) investigated the protective effect of metformin on kidney injury in mice model treated with a high fat diet. Metabolic disorders in a metformin treated group were significantly improved and the renal lipids deposition and other pathological changes were ameliorated. They also found the increase of expression of phospho-AMP-activated protein kinase (P-AMPK) α protein and the significant diminution of expression of sterol regulatory element-binding protein (SERBP)-1c and TNF-α (28). Similar effects regarding the activities of NAD(P)H and AMP-activated kinase have been observed after short-term activation of P2 receptors in podocytes. It is possible that, metformin induces the changes in AMPK and NAD(P)H oxidase activities by a mechanism involving P2 receptors, through increment of extracellular ATP concentration through inhibiting ecto-ATPase activity, hence leading to activation of the P2 receptors (18).

In CKD, kidney function associates more with the degree of tubulointerstitial damage than that of the glomerular abnormalities. In diabetic nephropathy, proteinuria may be one of the pathologic links among these two abnormalities (26,29). It has been proposed that microalbuminuria/proteinuria, angiotensin II, high blood sugar, AGE are capable to activate multiple signaling pathway in the proximal tubule epithelial cell (PTEC). Expression of a variety of chemokines, cytokines and adhesion molecules in PTEC leads to progressive tubular atrophy, interstitial fibrosis and inflammation (26-30). In addition, capillary rarefaction results local ischemia to the tubules, matrix protein deposition, more pro-fibrogenic mediators, fibrosis, and worsening of glomerulosclerosis. Therefore, DKD is often associated with glomerular changes, tubular cell degeneration, apoptosis, atrophy and finally interstitial fibrosis (31,32).

Clinical points of view

It has been shown that metformin reduces macrovascular complications and mortality in individuals with type 2 diabetes mellitus compare to the group treated with sulphonylurea derivatives or insulin (11). The reasons for this difference are not fully understood. In meta-analysis of 41 studies comprising 3074 patients, the metformin group had significantly lower plasma total cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride and HbA1C compared to the control group. However, it had no significant effects on high-density lipoprotein (HDL) cholesterol and blood pressure (33). It is worthy of note that any reduction in HbA1C will significantly decrease the risk of microvascular and macrovascular complications (34,35). Metformin may enhance the thrombolysis and the plasminogen activator inhibitor 1 in type II diabetic patients and also reduces non-enzymatic glycation (12,36,37).

Conclusion

It appears that metformin has multiple roles in protecting the kidney in diabetic patients. Tubular cell protection, improving hypertension, albuminuria and restoring the glomerular podocytes improves overall DKD outcome. It may be justified to use metformin for nephron-protection in early stage of DKD. Further clinical investigation on this subject is needed.

Authors' contribution

All authors wrote the manuscript equally.

Conflicts of interests

The authors declared no competing interests.

Ethical considerations

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

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