JOJ
Urology & Nephrology
ISSN: 2476-0552

Juniper Publishers
key to the Researchers

Mini Review
Volume 3 Issue 5 – July 2017
DOI: 10.19080/JOJUN.2017.03.555622

JOJ uro & nephron

Experimental and Alternative Therapy Targeting Oxidative Stress in Diabetic Kidney Disease: A Mini-Review

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Submission: July 13, 2017; **Published:** July 21, 2017

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Abstract

Diabetic kidney disease (DKD) has a prevalence of 20-40% of patients with chronic kidney disease. The increased urinary albumin excretion of ≥30mg/g creatinine and/or a Glomerular Filtration Rate (eGFR) <60mL/min/1.73m2 are considered abnormal. The main target for prevention and management of DKD is glycemic control, normalization of blood pressure, smoking cessation, reduction of salt intake, and prevention of infections for avoiding the fast increase of albuminuria or reduction of eGFR. Free radicals overproduction, dysfunctional growth factors, and increased inflammatory cytokines are identified as contributing pathophysiological changes that induce DKD. The glycemic control and cardiovascular risk reduction remain the cornerstones of mortality reduction of patients with DKD. Melatonin, resveratrol, tannins and coenzyme-Q10 are some attractive alternatives in the adjuvant management of inflammation and oxidative stress in DKD.

Keywords: Diabetic kidney disease; Chronic kidney disease; Oxidative stress; Antioxidants; Cardiovascular risk

Abbreviations: DKD: Diabetic Kidney Disease; CKD: Chronic Kidney Disease; DM: Diabetes Mellitus; eGFR: estimation of Glomerular Filtration Rate; PKC: Protein Kinase C; AGEs: Advanced Glycation End Products; TNF-α: Tumor necrosis factor-α; NFκB: Nuclear Factor Kappa B; TGF-ß: Transforming growth factor-ß; GPx: Glutathione Peroxidase; SOD: Super Oxide Dismutase; NAG: N-Acetyl-β-D-Glucosaminidase; STZ: Streptozotocin; MDA: Malondialdehyde; NO: Nitric Oxide; CoQ10: Coenzyme Q10; CAT: Catalase; GSH: Glutathione; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; EGCG: Epigallocatechin Gallate; HP: Hypercom Perforatum; ROS: Reactive Oxygen Species

Introduction

Diabetic Kidney Disease (DKD), the most recently adopted term for Chronic Kidney Disease (CKD) in patients with Diabetes Mellitus (DM): it has a prevalence of 20-40% in this group, and leads to an overall Hazard Ratio of 3.16 (95% CI 3.0,3.4) for all-cause mortality adjusted by age and sex, compared to the general population in some countries [1,2]. Early recognition of clinical changes include screening for albuminuria performed by urinary albumin-to-creatinine ratio in a random spot urine collection, and estimation of Glomerular Filtration Rate (eGFR). An increased urinary albumin excretion of ≥30mg/g Cr and/or an eGFR<60ml/min/1.73m2 are considered abnormal [3]. The main target for prevention and management of DKD is glycemic control, normalization of blood pressure, smoking cessation, reduction of salt intake, and prevention of infections that may precipitate a fast increase of albuminuria or reduction of eGFR [4,5]. Structural and pathological changes observed in DKD are increased glomerular basement membrane width, diffuse mesangial sclerosis, hyalinosis, microaneurysm, and hyaline arteriosclerosis. Forty to 50% of patients developing proteinuria have Kimmelstiel-Wilson nodules, defined as areas of extreme mesangial expansion [5].

The following review aims to describe novel therapeutic approaches for DKD in experimental studies focusing on alternative natural compounds. We include the most recent evidence for different outcomes related to oxidative stress and antioxidant status.

Oxidative stress and inflammation in DKD

The main pathways involved in the development of DKD are similar to diabetic retinopathy and neuropathy, such as

formation of advanced glycation end products (AGEs), polyol, hexosamine, and protein kinase C (PKC). On the other hand, free radicals overproduction, dysfunctional growth factors, and increased inflammatory cytokines are clearly identified as contributing pathophysiological changes that induce DKD [6]. These intimately correlated mechanisms can beclassified into four main pathways:

- Over expression of free radicals stimulate cytokine production via activation of interleukins
- Tumor necrosis factor-α (TNF-α) promote nuclear factor kappa B (NFκB) augmentation, generating an increase of monocyte chemoattractant protein-1 and finally overproduction of cellular adhesion molecules
- Nitric oxide (NO) reduction enhances peroxynitrite formation, thus, inducing endothelial dysfunction
- Transforming growth factor-ß (TGF-ß) increase the connective tissue growth factor and produce extracellular matrix deposition and fibrosis [7].

Ideal glucose lowering treatment in DKD

Glycemic control and cardiovascular risk reduction remain the cornerstones of mortality reduction of patients with DKD, thereby, it is fundamental to establish a dose-adjusted drug regimen in such individuals or selection of a more secure oral anti-diabetic in those without insulin treatment [8]. Available medication that does not require dose adjustment are pioglitazone, liraglutide, dulaglutide and linagliptin. On the other hand, metformin, meglitinides, lixisenatide, albiglutide, sitagliptin, saxagliptin and alogliptin require a dose reduction if GFR is less than 45mL/minper 1.73m2 in most cases, and <60ml/minper 1.73m2 in some of them. Usually, guidelines do not recommend initiation or continuing sulfonylureas, a-Glucosidase inhibitors, exenatide, and sodium-glucose cotransporter 2 inhibitor in patients with reduced GFR [8,9].

Experimental therapy in DKD

Melatonin stimulates the activity or gene expression of glutathione peroxidase (GPx), super oxide dismutase (SOD) and xanthine oxidase. Oktem et al. compared melatonin 10mg/kg per day in streptozotocin (STZ)-induced diabetic rats and demonstrated a significant reduction of renal malondialdehyde (MDA) content, urinary N-acetyl-β-D-glucosaminidase (NAG)/creatinine and microalbuminuria [10].

Coenzyme Q10 (CoQ10) loaded in liposomes showed benefit in type 1 diabetes-induced rats by reducing 24-h urinary protein, modulating oxidative stress indexes (MDA as oxidative biomarker and SOD as antioxidant), and preventing mitochondrial dysfunction with doses of 10mg/kg/day [11]. When combined with sitagliptin, CoQ10 had a more potent effect on MDA attenuation and reduced glutathione level (GSH), catalase (CAT) and SOD elevation in STZ-nicotinamide-induced diabetic nephropathy [12].

Resveratrol improved oxidative stress in diabetic rats alone and combined with rosuvastatin, although Hussein et al. [13]. Reporteda more potent effect of resveratrol when compared with rosuvastatin. With doses of 5mg/kg/day of resveratrol, a significant decrease of MDA levels, and increase of endogen antioxidants such as GSH, CAT, SOD and GPx was observed [13]. It can modulate different pathways of the forehead transcription factor and ameliorate the hyperglycemia-induced renal tubular oxidative stress damage [14].

Another beneficial natural compound, pomegranate seed oil, decreases renal tissue MDA content, serum creatinine and urea levels in experimental models after 3 and 4 weeks of treatment. It also demonstrated a reduction on urine protein, glucose and volume with 0.4 and 0.8ml/kg, and relevant biochemical markers such as serum glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C), and C-reactive protein, along with increase of high-density lipoprotein cholesterol (HDL-C) when the highest dose was administered [15].

Catechins are potent antioxidants contained in different plants and seeds. Epigallocatechin gallate (EGCG) is the most abundant and effective green tea catechin, and it has renoprotective effects by reducing MDA, TGF-β and many other proinflammatory and adhesion molecules [16].

Inhibition of AGEs can be achieved with petroleum ether and hydro-alcoholic extract of Linum usitatissimum or flax seed. The experimental study by Kaur et al. [17]. Proved that flax seed petroleum and hydro-alcoholic extracts produced significant attenuation in the glycemic status, renal biochemical parameters (urea, creatinine, blood urinary nitrogen), lipid profile and antioxidant enzymes after a 45-days treatment in STZ- nicotinamide induced diabetic nephropathy, with better results with higher doses (400mg/kg) [17].

The medicinal cracked-cap polypore mushroom Phellinus rimosus improved the activity of Krebs cycle dehydrogenases, mitochondrial electron transport chain complexes and ATP levels after a 30-day treatment with 250mg/kg/day in STZ-induced diabetic rat. Rony et al. [18] showed protection of the renal mitochondrial antioxidant status (SOD, GSH, glutathione peroxidase) and a more potent reduction of lipid peroxidation levels when compared to gliclazide 1mg/kg/day [18].

Hypercom perforatum (HP), known as St. John's wort, possesses potent antioxidant and anti-inflammatory properties due to the presence of naphthodianthrones, flavonoids, hyperforin and tannins. In 2017, Abd El Motteleb and Abd El Aleem [19]. Demonstrated the renoprotective effects of HP due to reduction of oxidative/nitrosative stress, enhancement of antioxidant defense mechanisms, decline of inflammatory cytokines, anti-fibrotic, anti-apoptotic and blood glucose with 200mg/kg/day [19].

Naringin is a flavanone widely distributed in grapefruit and oranges with anti-inflammatory, anti-apoptotic and antioxidant/

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free radical scavenging properties. Zhang et al [6]. Proved that naringin exerts a significant reduction of MDA and reactive oxygen species (ROS) as oxidative biomarkers in STZ-induced diabetic nephropathy rats after 12weeks with different doses of the compound (20, 40 and 80mg/kg/day). It also diminished apoptosis, blood glucose, BUN and urinary protein as biochemical markers. Finally, naringin increased GSH and SOD in kidney tissue, demonstrating its antioxidant effect [20].

Several other therapies have been mentioned before due to their antioxidant properties, such as curcumin, ginger, guava, grape seed, Ginkgo biloba, calycosin, cinnamon, garlic, black seed, ginseng, vitamin C and E, among others [21]. The large amount of experimental studies emphases the need for renoprotective substances to prevent oxidative damage to the kidney as part of an attempt to reduce the prevalence of DKD. Even though, in experimental models, these products have shown beneficial effects on oxidative stress homeostasis, there are few clinical trials in this pathology. More information is needed from prospective studies in humans beings to establish if the antioxidant therapies may be a plausible treatment for early DKD.

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