

Role of Oxidative Stress and Inflammatory Factors in Diabetic Kidney Disease

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Diabetic nephropathy (DN) is a serious complication of diabetes mellitus, and its prevalence has been increasing in developed countries. Diabetic nephropathy has become the most common single cause of end-stage renal disease (ESRD) worldwide. Oxidative stress and inflammation factors are hypothesized to play a role in the development of late diabetes complications. Chronic hyperglycemia increases oxidative stress, significantly modifies the structure and function of proteins and lipids, and induces glycooxidation and peroxidation. Therefore, hyperglycemia causes auto-oxidation of glucose, glycation of proteins, and activation of polyol mechanism. Overproduction of intracellular reactive oxygen species contributes to several microvascular and macrovascular complications of DN. On the other hand, reactive oxygen species modulates signaling cascade of immune factors. An increase in reactive oxygen species can increase the production of inflammatory cytokines, and likewise, an increase in inflammatory cytokines can stimulate the production of free radicals. Some studies have shown that kidney inflammation is serious in promoting the development and progression of DN. Inflammatory factors which are activated by the metabolic, biochemical, and hemodynamic derangements are known to exist in the diabetic kidney. This review discusses facts for oxidative stress and inflammatory factors in DN and encompasses the role of immune and inflammatory cells, inflammatory cytokines, and stress oxidative factors.

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INTRODUCTION

Diabetic nephropathy (DN) is considered as one of the main microvascular complications of diabetes mellitus (DM) and has become the most general single cause of end-stage renal disease (ESRD) worldwide.¹⁻⁶ It is traditionally defined a progressive rise in urine albumin excretion together with increasing blood pressure, leading to declined glomerular filtration, and eventually ESRD.⁷⁻⁹ It also is characterized by renal morphological and functional alterations such as glomerular hyperfiltration, glomerular and renal hypertrophy,

increased urinary albumin excretion, increased basement membrane thickness, and mesangial expansion with the accumulation of extracellular matrix proteins such as collagens, fibronectin, and laminin.¹⁰⁻¹²

On the one hand, there are several risk factors for the development of DN, including duration of DM, age at diagnosis, race, systemic or glomerular hypertension, poor glycemic control, genetic predisposition to kidney disease, and dietary composition. On the other hand, oxidative stress and inflammatory factors are 2 serious elements

in promoting DN. Subsequently, nephropathy is a common microvascular complication among patients with type 2 DM and a major cause of chronic kidney disease.¹³⁻²⁰

This review article discusses the pathophysiological mechanisms of renin-angiotensin system (RAS) inhibition by herbal plants. For this review, we used a variety of sources by searching through the Web of Science, PubMed, EMBASE, Scopus, and the Directory of Open Access Journals (DOAJ). The search was performed using combinations of the following key words and their equivalents: *diabetic nephropathy, reactive oxygen species, chronic kidney disease, microalbuminuria, and advanced glycation end products*.

PATHOGENESIS OF DIABETIC NEPHROPATHY

The development of DN has been described as a 5-stage process: stage 1, progression of glomerular hyperfiltration and nephromegaly and an above-normal glomerular filtration rate (GFR); stage 2, thickening of glomerular basement membrane and mesangial expansion, with GFR remaining elevated or returned to normal, but glomerular damage progressed to significant microalbuminuria (excreting more than 30 mg of albumin in urine over a 24-hour period); stage 3, progression of microalbuminuria (more than 300 mg of albumin in a 24-hour period), eventual decline in GFR and hypertension; stage 4, continued glomerular damage, overt proteinuria, increased blood urea nitrogen and creatinine, decreased GFR by about 10% annually with severe hypertension and sequelae of moderate to severe renal insufficiency; and stage 5, fibrosis, sclerosis, decreased GFR to approximately 10 mL/min, and eventual ESRD.¹³⁻²⁰

PATHOPHYSIOLOGY PATHWAYS

There are different pathways such as formation of advanced glycation end products, polyol pathway, hexosamine pathway, protein kinase C pathway, growth factors, cytokines, and free radicals that have been reported to play an important role in DN.²⁰⁻²²

Advanced Glycation End-products Pathways

Hyperglycemia has generally been considered as the key initiator of kidney damage, which can act by activation and dysregulation of several

metabolic pathways. Some evidence demonstrates that advanced glycation end products (AGEs) play a pivotal role in the development and progression of diabetic vascular damage. Additionally, diabetic patients with ESRD had almost twice as much AGEs in the kidneys as diabetic patients without kidney disease. Accumulation of AGEs in the kidney may contribute to the progressive alteration in and loss of kidney function in the patients. Advanced glycation end products contribute to a variety of microvascular and macrovascular complications through the formation of cross-links between molecules in the basement membrane of the extracellular matrix and by engaging the receptor for advanced glycation end products.²³⁻²⁵ Therefore, AGEs can alter intracellular signaling, gene expression, release of pro-inflammatory molecules, and free radicals. Consequently, increasing levels of AGEs support the formations of reactive oxygen species (ROS) and reactive nitrogen species (RNS) which in turn induce further formation of AGEs. On the other hand, AGEs formation can connect with key molecules in the basement membrane of the extracellular matrix (ECM), including lipids, collagen, laminin, elastin, and vitronectin; therefore, formation of AGEs on ECM molecules alters the constitution of the matrix, both matrix-matrix and cell-matrix interactions, being involved in signaling pathway of diabetic glomerulosclerosis.²⁶⁻³⁰

The main site for reabsorption of filtered AGEs is proximal tubule of kidney. Accumulation of AGEs in the kidney can induce transforming growth factor (TGF)- β gene expression possibly via protein kinase C (PKC) or oxidative stress pathway. Some studies show oxidative stress is increased in proportion to the accumulation of AGEs; also, these compounds can lead to enhanced formation of free radicals.^{25,28}

Based on recent evidence, AGEs and carbonyl intermediates contribute to the generation of superoxide from mitochondrial system; therefore, AGEs contribute to the release of pro-inflammatory cytokine and expression of growth factors such as TGF- β , insulin-like growth factor 1, platelet-derived growth factor, tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , and IL-6.^{30,31}

Polyol Pathway

Increasing the amount of nonconsumption glucose induces polyol pathway, which can increase AGEs

formation and oxidative stress factors. Therefore, hyperglycemia can induce polyol pathway flux.³²⁻³⁴ The polyol pathway consists of 2 enzymes: aldose reductase that reduces glucose to sorbitol with assistance of its cofactor nicotinamide adenine dinucleotide phosphate (NADPH), and sorbitol dehydrogenase (SDH) that converts sorbitol to fructose with assistance its co-factor NAD⁺. These enzymes decrease the ratio of NADPH/NADP and increase the ratio of NADH/NAD; thus, these may result in both oxidative stress and activation of PKC. Based on evidence, NADPH acts as a cofactor for glutathione reductase, which is significant for equilibrium of ROS. On the other hand, sorbitol cannot diffuse easily across cell membranes and it induces osmotic damage to microvascular cells. Generally, it is suggested that increased flux of glucose metabolism through the polyol pathway can induce activation of PKC, reduction of NADPH, and amplification of ROS.³⁵⁻³⁸

Hexosamine Pathway

Excessive intracellular glucose can induce activation of hexosamine pathway, in which fructose-6-phosphate is diverted from glycolysis to glucosamine-6-phosphate and other substrates for reactions that require uridine diphosphate -N-acetylglucosamine. Based on evidence, glutamine-fructose-6-phosphate amidotransferase (GFAT) is the rate-limiting enzyme of this pathway. Both high glucose and angiotensin II activates the GFAT promoter in mesangial cells. Increasing of glucose metabolism flux through the hexosamine pathway can induce overexpression of *GFAT* gene in mesangial cells that to enhances both TGF- β and fibronectin expression. Although the mechanism by which overexpression is induced is uncertain, it has been supposed the mechanism is by increased N-acetylglucosamine that may covalently modify transcription factors and signaling molecules. Also, N-acetylglucosamine can activate PKC and all factors which are associated with the development of DN.³⁹⁻⁴¹

Protein Kinase C Pathway

Protein kinase C is activated by excessive diacylglycerol, lipid second messenger, which is formed from glyceraldehyde-3-phosphate. Based on evidence, hyperglycemia can induce increased amount of diacylglycerol in cultured microvascular

cells and in the retina and renal glomeruli of diabetic animals.⁴²⁻⁴⁵ In the kidney, PKC activation can reduce production of nitric oxide by endothelial nitric oxide synthase; therefore, it leads to changes in renal blood flow, mesangial expansion, albuminuria and increased GFR, increased pro-inflammatory gene expression, and vascular permeability.^{5,9} Also, PKC activation may be responsible for the amplified expression of ECM molecules both directly and through TGF- β 1 overexpression. Some studies show that PKC activation induces expression of the permeability-enhancing factor vascular endothelial growth factor (VEGF) in smooth muscle cells, which contributes to increased microvascular matrix protein accumulation by inducing expression of TGF- β , fibronectin, and type IV collagen. In addition, PKC activation has also been implicated in the overexpression of the fibrinolytic inhibitor plasminogen activator inhibitor-1, activation of nuclear factor- κ B in cultured endothelial cells and vascular smooth muscle cells.^{42,46}

Growth Factors and Cytokines

Hyperglycemia stimulates resident and nonresident renal cells to produce several growth factors, cytokines, chemokines, and vasoactive agents that implicate to the development of kidney injury. Growth factors which are involved in the development of DN include VEGF, Platelet Derived Growth Factor, Connective Tissue Growth Factor (CTGF), and insulin-like growth factor.⁴⁶⁻⁵²

Transforming Growth Factor- β

Tumor growth factor B, a profibrogenic cytokine, which controls synthesis and degradation of extracellular matrix proteins by stimulating transcription of *ECM* genes in renal cells and reducing collagenase production, eventually plays a central role in the development of renal hypertrophy and accumulation of ECM components. Therefore, monocytes, macrophages, and macrophages are filtrated into glomeruli and they release growth factors and cytokines that may contribute to promotion of glomerular growth.⁵³

There is increasing evidence that factors such as hyperglycemia, AGEs, endothelin, and products of oxidative stress regulate TGF- β gene expression in renal cells. Also, it is obvious that intrarenal RAS is activated in DN. In fact, angiotensin II stimulates TGF- β gene expression in renal cells by molecular

mechanism. Therefore, enhanced expression of angiotensin II receptors and decreased degradation of angiotensin II involved in many biological processes that local effects of angiotensin II which acts in synergy with hyperglycemia in stimulating free radicals can induce renal hypertrophy and synthesis of ECM proteins.^{40,44}

Connective Tissue Growth Factor

Connective tissue growth factor has been described as a marker and a mediator of DN. Synthesis of CTGF is stimulated by hyperglycemia, AGEs, and TGF- β . Connective tissue growth factor induces mesangial cell hypertrophy and cytoskeletal disassembling and upregulates cell production of fibronectin and collagens.⁴⁵ Also, CTGF is an important mediator of the profibrotic activity of TGF- β .

Vascular Endothelial Growth Factor

Vascular Endothelial Growth Factor is a potent inducer of vasopermeability and angiogenesis that plays a major pathophysiological role in DN. Serum levels of VEGF associate with albuminuria and increase with DN stage. Several studies have confirmed that VEGF may contribute to some of the hemodynamic alterations in DN, including hyperfiltration and albuminuria. Expression of VEGF is modulated by high glucose, endothelin 1, AGEs, angiotensin II, and TGF- β . Also, VEGF can affect podocyte function and involves in macrophage influx into glomeruli.^{44,46}

Oxidative Stress

Reactive oxygen species, such as superoxide or hydroxyl, are byproducts of oxygen metabolism that play a major part in cell signaling and degenerative disease processes. Naturally, the quantity of ROS produced is balanced with the anti-oxidant activity including, superoxide dismutase, catalase, and glutathione peroxidase that are required for neutralizing its adverse effects. Therefore, ROS is continuously generated but effectively eliminated by antioxidant activity system. Imbalance of ROS generation with antioxidant system can alter essential cellular proteins or DNA.^{37,38} Also, ROS generation may be increased through multiple mechanisms including increased polyol pathway, AGEs formation, NADPH oxidase and activation of PKC. Nicotinamide adenine dinucleotide

phosphate oxidase is the main source of ROS in the mesangial cells, smooth cells, and endothelial cells. Hyperglycemia induces oxidative stress that increases generation of ROS or diminishes the production of antioxidants that can lead to increased oxidant-derived tissue injury.³⁵ Some evidence show high glucose can induce activation of PKC in diabetic glomeruli through de novo synthesis of diacylglycerol. Also, PKC produces ROS which in turn causes activation of PKC thereby causing augmentation of mesangial expansion, basement membrane thickening, and dysfunction of endothelial cells, leading to DN.¹⁸⁻²⁰ Hyperglycemia activates isoforms of nicotinamide adenine dinucleotide phosphate oxidases, especially nicotinamide adenine dinucleotide phosphate oxidases-4 that induces ROS formation thereby leads to endothelial dysfunction, inflammation, and apoptosis.^{39,40}

Furthermore, it has been found that ROS activates PKC, mitogen activated protein kinase, NADPH oxidase, and nuclear factor- κ B, and upregulates TGF- β 1 and fibronectin levels; thus, production of ROS in DN can induce renal tissue injury. Therefore, enhanced level of TGF- β leads to renal hypertrophy, glomerulosclerosis, and tubulointerstitial fibrosis in DN.⁴⁷⁻⁴⁹

Some studies suggest that VEGF, a protein factor secreted by the podocytes and the mesangial cells of the kidney, plays an important function in the progression of DN. In oxidative stress condition, VEGF gene expression is increased by the activity of hypoxia-inducible factor that interferes with the phosphoinositide 3-kinase/protein kinase B pathway and modulates the expression of endothelial nitric oxidase synthase. Therefore, VEGF ultimately elevates the level of intracellular ROS by stimulating the generation of peroxynitrite. In addition, VEGF leads to the proteinuria thereby adding complications to DN.^{46,50}

Consequently, hyperglycemia increases the inflammatory activities by activating macrophages follow by enhances ROS production leading the way to DN. Some evidences show excessive ROS production by different pathways leads to the activation of downstream molecules such as p38 mitogen activated protein kinases, nuclear factor- κ B, and TGF- β pathways. Generally, hyperglycemia elevates intracellular ROS by many converging pathways and finally leads to nephropathic situation by activating an array of

diverging signaling cascades. Also, ROS-regulated signaling pathways lead to accumulation of ECM in the kidney tissue.^{21,37,48}

Inflammation Cells and Inflammatory Factors

From the beginning of stages of DN, macrophages and T cells accumulate in the glomeruli and interstitium. Activated macrophages, key inflammatory cells of the kidney, elaborate a host of pro-inflammatory, pro-fibrotic, and antiangiogenic factors. These macrophage-derived products include TNF- α , IL-1, IL-6, ROS, plasminogen activator inhibitor-1, matrix metalloproteinases, TGF- β , platelet-derived growth factor, angiotensin II, and endothelin.³²⁻³⁴ Hyperglycemia induces macrophage accumulation and activation that can deposit glomerular immune complex, increase chemokine production, and progressive fibrosis. Some evidence show kidney macrophage accumulation is strongly associated with the degree of glomerular sclerosis, creatinine serum levels, proteinuria, and interstitial fibrosis. Monocyte chemoattractant protein 1, a key cytokines involved in macrophage migration into the diabetic kidney, is significantly increased in DN. Some studies suggest that renal chemoattractant protein 1 is also correlated with proteinuria.^{3,8,47,48}

Lymphocytes

T cells can also infiltrate into diabetic kidneys, and their function is better characterized in crescentic glomerulonephritis, for instance antiglomerular basement membrane disease. In diabetic patients, T cell influx into kidney correlates with altered kidney function and albuminuria. Some evidence note T cells accumulate in the juxtaglomerular apparatus although; the functional role of T cells in this compartment is unclear.^{5,9,11}

Intercellular adhesion molecule (ICAM)-1, a glycoprotein involved in attachment of leukocytes to endothelium, associates with leukocyte infiltration and disease progression in diabetic patients. Intercellular adhesion molecule-1 expression is induced by factors such as hyperglycemia, AGEs, and andoxidative stress, but it can also be increased by additional elements such as hyperlipidemia, hyperinsulinemia, and elevated levels of circulating TNF- α . Also, it is demonstrated that intercellular adhesion molecule-1 is a critical mediator of macrophage accumulation in diabetic kidneys both in early and late stages of diabetes.^{4,10,46}

Tumor necrosis factor- α is generally produced by monocytes, macrophages, and T cells. Also, it can be generated by resident renal cells including mesangial, glomerular, endothelial, dendritic, and renal tubular cells. Tumor necrosis factor- α induces production of local ROS, increasing albumin permeability, induction of cytotoxicity, apoptosis, and necrosis. Some studies demonstrate patients with type 2 diabetes have 3 to 4 times greater serum levels of TNF- α compared to nondiabetic patients. The amount of TNF- α serum levels is correlated with microalbuminuria in diabetic patients. However, TNF- α is a clinical markers of DN and progression of disease.⁴⁷⁻⁴⁹

Interleukin-1 induces expression of chemotactic factors and adhesion molecules, enhances vascular endothelial permeability, and stimulates the proliferation of mesangial cells. Some studies demonstrate IL-1 increases endothelial cell permeability and alters glomerular hemodynamics by affecting prostaglandin synthesis therefore; it can stimulate mesangial and fibroblast proliferation. Interleukin-1 levels correlate with albuminuria and end-stage kidney disease.^{18-22,52}

Interleukin 6 is a pleiotropic cytokine secreted by endothelial cells, leukocytes, adipocytes, and mesangial cells. It can affect extracellular matrix dynamics in renal cells and enhances endothelial permeability.⁵³ Serum IL-6 levels have a significant correlation with severity of diabetic glomerulopathy, kidney hypertrophy, and albumin excretion thus suggested a role for IL-6 in the pathogenesis of DN. It has been suggested that IL-6 mediates endothelial permeability, mesangial proliferation, and increased fibronectin expression.⁵³

Interleukin-18

Interleukin-18, a potent inflammatory cytokine, induces interferon- γ expression and the production of other pro-inflammatory cytokines such as IL-1 and TNF- α . Also, it upregulates intercellular adhesion molecule-1 in endothelial cells. Some studies demonstrate tubular epithelial cells, infiltrating monocyte-macrophages and T cells are the major sources of IL-18. It is revealed serum and urinary IL-18 levels increase in DN and correlate with microalbuminuria. In addition, there is a positive association between serum IL-18 levels with urinary excretion of beta-2 microglobulin (a marker of tubulointerstitial injury).⁵⁴⁻⁵⁸

CONCLUSIONS

Diabetic nephropathy has been described as a progressive increase in urine albumin excretion together with increasing blood pressure, leading to declined glomerular filtration and finally ESRD. The development of DN has been described as a 5-stage process. There are different pathways such as formation of advanced glycation end products, polyol pathway, hexosamine pathway, protein kinase C pathway, growth factors, cytokines, and free radicals that play an important role in creation and progression of diabetic nephropathy, according to latest studies.

CONFLICTS OF INTEREST

None declared.

REFERENCES

- Moradi M, Rahimi Z, Amiri S, et al. AT1R A1166C variants in patients with type 2 diabetes mellitus and diabetic nephropathy. *J Nephrothol*. 2015;4:69-76.
- Gheith O, Farouk N, Nampoory N, Halim MA, Al-Otaibi T. Diabetic kidney disease: worldwide difference of prevalence and risk factors. *J Nephrothol*. 2016;5:49-56.
- Akbari F, Shahinfard N, Mirhoseini M, Shirzad H, Heidarian E, Hajian S, Rafeian-Kopaei M. Impacts of *Hibiscus esculentus* extract on glucose and lipid profile of diabetic rats. *J Nephrothol*. 2016;5:80-85.
- Adeshara KA, Diwan AG, Tupe RS. Diabetes and Complications: Cellular Signaling Pathways, Current Understanding and Targeted Therapies. *Curr Drug Targets*. 2016;17:1309-28.
- Asadi-Samani M, Bahmani M. Trends on the treatment of atherosclerosis; new improvements. *Angiologica Persica Acta*. 2016;1:e01.
- Tavafi M, Hasanvand A, Ashoory H. Proximal convoluted tubule cells in ischemia and post injury regeneration. *Acta Persica Pathophysiol*. 2016;1:e05.
- Ng KP, Jain P, Gill PS, et al. Results and lessons from the Spironolactone to Prevent Cardiovascular Events in Early Stage Chronic Kidney Disease (STOP-CKD) randomized controlled trial. *BMJ Open*. 2016;6:e010519.
- Thomas MC. Epigenetic Mechanisms in Diabetic Kidney Disease. *Curr Diab Rep*. 2016;16:31.
- Sutaria A, Liu L, Ahmed Z. Multiple medication (polypharmacy) and chronic kidney disease in patients aged 60 and older: a pharmacoepidemiologic perspective. *Ther Adv Cardiovasc Dis*. 2016.
- Arévalo-Lorido JC, Carretero-Gómez J, García-Sánchez F, et al. Secondary hyperparathyroidism prevalence and profile, between diabetic and non-diabetic patients with stage 3 to 4 chronic kidney disease attended in internal medicine wards. MIPTH study. *Diabetes Metab Syndr*. 2016.
- Nazar CMJ, Bojerenu MM. Diabetes education. *J Renal Endocrinol*. 2016;2:e02.
- Sun L, Dutta RK, Xie P, et al. Myoinositol Oxygenase Over-Expression Accentuates Generation of Reactive Oxygen Species and Exacerbates Cellular Injury Following High Glucose Ambience: A New Mechanism Relevant to the Pathogenesis of Diabetic Nephropathy. *J Biol Chem*. 2016.
- Amiri M, Hosseini SM. Diabetes mellitus type 1; is it a global challenge? *Acta Epidemiocriinol*. 2016;1:e02.
- McClelland AD, Herman-Edelstein M, Komers R, et al. miR-21 promotes renal fibrosis in diabetic nephropathy by targeting PTEN and SMAD7. *Clin Sci (Lond)*. 2015;129:1237-49.
- Tolouian R, Hernandez G. Prediction of diabetic nephropathy: The need for a sweet biomarker. *J Nephrothol*. 2013;2:4-5.
- Badal SS, Danesh FR. Diabetic Nephropathy: Emerging Biomarkers for Risk Assessment. *Diabetes*. 2015;64:3063-5.
- Amiri M. Type 2 diabetes mellitus; an international challenge. *Ann Res Dial*. 2016;1:e04.
- Tavafi M. *Hibiscus esculentus* against hyperglycemia and dyslipidemia. *Ann Res Antioxid*. 2016;1:e26.
- Hajian S, Asgary S, Rafeian-Kopaei M, et al. *Hibiscus esculentus* seed and mucilage beneficial effects in reducing complications of diabetes in streptozotocin-induced diabetic rats. *Ann Res Antioxid*. 2016;1:e23.
- Rahimi Z, Mansouri Zaveleh O, Rahimi Z, Abbasi A. AT2R -1332 G: A polymorphism and diabetic nephropathy in type 2 diabetes mellitus patients. *J Renal Inj Prev*. 2013;2:97-101.
- Roshan B, Stanton RC. A story of microalbuminuria and diabetic nephropathy. *J Nephrothol*. 2013;2:234-40.
- Elshebiny NM, Al-Gayyar MM. The role of IL-18 in type 1 diabetic nephropathy: The problem and future treatment. *Cytokine*. 2016;81:15-22.
- Sutariya B, Jhonsa D, Saraf MN. TGF- β : the connecting link between nephropathy and fibrosis. *Immunopharmacol Immunotoxicol*. 2016 Feb;38:39-49.
- Yao F, Zhang M, Chen L. 5'-Monophosphate-activated protein kinase (AMPK) improves autophagic activity in diabetes and diabetic complications. *Acta Pharm Sin B*. 2016;6:20-5.
- Sönmez MF, Dündar M. Ameliorative effects of pentoxifylline on NOS induced by diabetes in rat kidney. *Ren Fail*. 2016;38:605-13.
- Dehghan Shahreza F. An update on oxidative stress and diabetic kidney disease. *Immunopathol Persa*. 2015;1:e30.
- Kikuchi H, Kanda E, Mandai S, et al. Combination of low body mass index and serum albumin level is associated with chronic kidney disease progression: the chronic kidney disease-research of outcomes in treatment and epidemiology (CKD-ROUTE) study. *Clin Exp Nephrol*. 2016 Feb 26. [Epub ahead of print]
- Hajian S. Positive effect of antioxidants on immune system. *Immunopathol Persa*. 2015;1:e02.
- Nasri H, Abedi-Gheshlaghi Z, Rafeian-Kopaei M.

- Curcumin and kidney protection; current findings and new concepts. *Acta Persica Pathophysiol.* 2016;1:e01.
30. Dehghan Shahreza F. Renal tubular cell injury and its protection by antioxidants; new trends. *J Inj Inflamm* 2016;1:e01.
 31. Kafeshani M. Ginger, micro-inflammation and kidney disease. *J Renal Endocrinol.*2015;1:e04.
 32. Jagdale AD, Bavkar LN, More TA, et al. Strong inhibition of the polyol pathway diverts glucose flux to protein glycation leading to rapid establishment of secondary complications in diabetes mellitus. *J Diabetes Complications.* 2016;30:398-405.
 33. Shahbazian H. World diabetes day; 2013. *J Renal Inj Prev.* 2013;2:123-4.
 34. Hosseini M, Amini M, Roosta S, Farazandemehr A. Trends of serum creatinine among patients with type 2 diabetes in Isfahan endocrine and metabolism research center; a longitudinal study. *J Prev Epidemiol.* 2016;1:e10.
 35. Dehghan Shahreza F. Vascular protection by herbal antioxidants; recent views and new concepts. *J Prev Epidemiol.* 2016;1:e05.
 36. Mirhoseini M, Baradaran A, Rafeian-Kopaei M. Medicinal plants, diabetes mellitus and urgent needs. *J HerbMed Pharmacol.* 2013;2:53-4.
 37. Nayak BK, Shanmugasundaram K, Friedrichs WE, et al. HIF-1 mediates renal fibrosis in OVE26 type 1 diabetic mice. *Diabetes.* 2016;65:1387-97.
 38. Dehghan Shahreza F. Hibiscus esculentus and diabetes mellitus. *J Nephropharmacol.* 2016;5:104-5.
 39. Oikari S, Makkonen K, Jawahar Deen A, et al. Hexosamine biosynthesis in keratinocytes - roles of GFAT and GNPDA enzymes in the maintenance of UDP-GlcNAc content and hyaluronan synthesis. *Glycobiology.* 2016;26:710-22.
 40. Ranjbar A, Ghasemi H, Hatami M, Dadras F, Heidary Shayesteh T, Khoshjou F. Tempol effects on diabetic nephropathy in male rats. *J Renal Inj Prev.* 2016;5:74-8.
 41. Luo X, Wu J, Jing S, Yan LJ. Hyperglycemic Stress and Carbon Stress in Diabetic Glucotoxicity. *Aging Dis.* 2016;7:90-110.
 42. Tobias IS, Kaulich M, Kim PK, et al. Protein kinase C ζ exhibits constitutive phosphorylation and phosphatidylinositol-3,4,5-triphosphate-independent regulation. *Biochem J.* 2016;473:509-23
 43. Nazar CMJ, Bojerenu MM, Safdar M, Marwat J. Effectiveness of diabetes education and awareness of diabetes mellitus in combating diabetes in the United Kingdom; a literature review. *J Nephropharmacol.* 2016;5:110-5.
 44. Nasri H, Rafeian-Kopaei M. Metformin improves diabetic kidney disease. *J Nephropharmacol.* 2012;1:1-2.
 45. Kafeshani M, Zarafshani M, Shokri-Moghaddam S, Ahmadi A, Nasri H. Serum 25-hydroxy vitamin D level in diabetic patients versus normal individuals; a pilot study. *J Parathyroid Dis.* 2016;4:40-3.
 46. Muhl L, Moessinger C, Adzemovic MZ, et al. Expression of vascular endothelial growth factor (VEGF)-B and its receptor (VEGFR1) in murine heart, lung and kidney. *Cell Tissue Res.* 2016;365:51-63.
 47. Tamadon MR. Secondary hyperparathyroidism and chronic kidney disease. *J Parathyroid Dis.* 2013;1:15-6.
 48. Nasri H. On the occasion of the world diabetes day 2013; diabetes education and prevention; a nephrology point of view. *J Renal Inj Prev.* 2013;2:31-2.
 49. Dehghan Shahreza F. From oxidative stress to endothelial cell dysfunction. *J Prev Epidemiol.* 2016;1:e04.
 50. Rafeian-Kopaei M, Baradaran A. On the occasion of world diabetes day 2105; act today to change tomorrow. *J Renal Endocrinol.* 2015;1:e02.
 51. Nasri H. Impact of diabetes mellitus on parathyroid hormone in hemodialysis patients. *J Parathyroid Dis.* 2013;1:9-11.
 52. Fallahzadeh MH, Fallahzadeh MA. On the occasion of world kidney disease 2016; renal disease in children. *Acta Persica Pathophysiol.* 2016;1:e04.
 53. Meng J, Li L, Zhao Y, et al. MicroRNA-196a/b Mitigate Renal Fibrosis by Targeting TGF- β Receptor 2. *J Am Soc Nephrol.* 2016;27:3006-21.
 54. Wu J, Han J, Hou B, et al. Sulforaphane inhibits TGF- β -induced epithelial-mesenchymal transition of hepatocellular carcinoma cells via the reactive oxygen species-dependent pathway. *Oncol Rep.* 2016;35:2977-83.
 55. Baharvand-Ahmadi B, Bahmani M, Tajeddini P, Naghdi N, Rafeian-Kopaei M. An ethno-medicinal study of medicinal plants used for the treatment of diabetes. *J Nephropathol.* 2016;5:44-50.
 56. Nasri H, Rafeian-Kopaei M. On the occasion of world kidney day 2016; work together to better protect the kidney. *J Nephropathol.* 2016;5:15-8.
 57. Baradaran A. Concepts towards endothelial dysfunction in diabetes mellitus. *Angiologica Persica Acta.* 2016;1:e02.
 58. Azadegan-Dehkordi F, Bagheri N, Shirzad H, et al. The role of Th1 and Th17 cells in glomerulonephritis. *J Nephropathol.* 2015;4:32-37.
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