The Role of Dietary Antioxidants on Oxidative Stress in Diabetic Nephropathy

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Diabetic nephropathy (DN) is the leading cause of end-stage renal disease and oxidative stress (OS) has been recognized as a key factor in the pathogenesis and progression. Hyperglycemia, reactive oxygen species, advanced glycation end products, arterial pressure, insulin resistance, decrease in nitric oxide, inflammatory markers, and cytokines, among others; are involved in the presence of OS on DN. This revision focus on diverse studies in experimental and human models with diabetes and DN that has been demonstrated beneficial effects of different dietary antioxidant as resveratrol, curcumin, selenium, soy, catechins, α-lipoic acid, coenzyme Q10, omega-3 fatty acids, zinc, vitamins E and C, on OS and the capacity for antioxidant response. Therefore, this interventions could have a positive clinical impact on DN.

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Review

INTRODUCTION

Diabetic nephropathy (DN) is a microvascular complication of diabetes mellitus (DM) and is the primary cause of end-stage renal disease (ESRD) worldwide.[1,2] On kidney biopsy, mesangial expansion and extracellular deposits is seen, leading to damage to the glomerular structure and enlargement of the glomerular membrane,

at the end of the process usually glomerular and interstitial fibrosis culminated with a dysfunctional nephron.[2] Oxidative stress (OS) is present in DM and hyperglycemia is the principal factor in the early, sustained generation of OS, which contributes to the pathogenesis of DN.[1] Other complications of hyperglycemia that promote OS include: the formation of advance glycation end products (AGEs), an increase in the generation of reactive oxygen species (ROS), the decrease in the production of nitric oxide (NO), and the activation of the protein kinase C (PKC), the polyol pathways, and the renin-angiotensin system.[1,3–7] The OS combined with hyperglycemia can generate negative repercussions on the structure and function of the kidney, increasing, at the glomerular level, endothelial cell dysfunction, the depositing of extracellular matrix, mesangial cell injury, dysfunction of the podocytes, the increase in transforming growth factor β (TGF-β), cellular apoptosis, and microalbuminuria. Also, in the tubules there is an increase in oxidative injury, hypoxia, fibrosis, apoptosis and proteinuria, and a decrease in NO and the hypoxia-inducible factor 1α.[1] Recommended therapies that can be useful in reducing OS and delay DN include good glycemia control, adequate levels of arterial pressure and lipids, exercise, smoking cessation, antioxidant agents, and diet, for example, with antioxidant foods.[1,8,9] Given that OS is implicated in the pathogenesis and progression of DN, antioxidant therapies that modulate this condition would favorably impact the course of the illness. Therefore, the objective of the current review is to determine the role of dietary antioxidants as a therapeutic intervention on OS in DN.

DIABETIC NEPHROPATHY

The DN is characterized by the presence of pathological quantities of the excretion or ratio of albumin/creatinine (mg/gr) in urine (A1, < 30; A2, 30 – 300; A3, > 300), diabetic glomerular lesions, and reduction of the glomerular filtration rate.[10,11] Pathological changes in DN like glomerular hypertrophy, thickening of the basement and the accumulation of extracellular matrix in the glomerular membranes and tubules, lead as much to fibrosis as to glomerular and tubulointerstitial sclerosis.[12,13] In Table 1, the classification of DN has been demonstrated.[14] As previously mentioned, DN is the primary cause of ESRD in the world; which is associated to an increase in cardiovascular morbidity and mortality.[1,15] The prevalence of this condition in type 1 and type 2 diabetic patients varies between 25 – 40%.[15] The risk factors for the development and progression of DN include: the markers of inflammation and oxidation, hyperglycemia, AGEs, ROS, profibrotic cytokines (TGF-β), an increase in PKC, abnormalities in metabolism of the polyols, uric acid levels, long history of DM, age at diagnosis, race, systemic or glomerular hypertension, albuminuria, genetic predisposition, insulin resistance, and dietary composition, among others.[7,15]

OXIDATIVE STRESS IN DIABETIC NEPHROPATHY

The imbalance between oxidants and antioxidants

Table 1. Classification of Diabetic Nephropathy[14]

Stage	Urinary Albumin (mg/g Cr) or Urinary Protein (g/g Cr)	GFR (eGFR) (mL/min/1.73m^2)
Stage 1 (Pre-nephropathy)	Normoalbuminuria (< 30)	≥ 30[a]
Stage 2 (Incipient Nephropathy)	Microalbuminuria (30 – 299)[b]	≥ 30
Stage 3 (Overt Nephropathy)	Macroalbuminuria (≥ 300) or persistent proteinuria (≥ 0.5)	≥ 30[c]
Stage 4 (Kidney Failure)	Any Albuminuria/Proteinuria Status[d]	< 30
Stage 5 (Dialysis Therapy	Any Status on Continued Dialysis Therapy	

[a] While a GFR of less than 60 mL/min/1.73 m^2 is consistent with the diagnosis of CKD, underlying causes other than diabetic nephropathy may be involved in patients with a GFR below 60 mL/min/1.73m^2 thus calling for the differential diagnosis between diabetic nephropathy and any other potential non-diabetic kidney diseases.
[b] Patients with microalbuminuria are to be diagnosed as incipient nephropathy after the differential diagnosis based on the criteria for an early diagnosis of diabetic nephropathy.
[c] Precautions are required in patients with macroalbuminuria, in whom renal events (e.g., a decrease in eGFR to half its baseline value, the need for dialysis) have been shown to increase as the GFR decreases below 60 mL/min/1.73m^2.
[d] All patients with a GFR of less than 30 mL/min/1.73m^2 are classified as exhibiting kidney failure, regardless of their urinary albumin/protein values. However, in those with normoalbuminuria and microalbuminuria, the differential diagnosis is required between diabetic nephropathy and any other potential non-diabetic kidney diseases.

in favor of the oxidants is called OS.[16] The kidneys perform multiple functions such as regulation of body fluids and blood pressure, excretion of waste products, and production of red globules. The kidney is conformed by multiple mitochondria, this makes it more vulnerable to the damage produced by the OS.[17] In DM factors like hyperglycemia, ROS, AGEs, arterial pressure, insulin resistance, decreased NO, inflammatory markers, and cytokines, among others, contribute to the pathogenesis of OS.[1] The intrarenal OS undertakes a critical role in the pathogenesis and progress of DN.[18] Given than this imbalance (pro-oxidant/antioxidant) is present in DN, there is an overproduction of ROS/reactive nitrogen species (RNS) and a decrease in antioxidant enzymes (manganese superoxide dismutase-MnSOD, glutathione peroxidase-GPx, and catalase).[4,19] The alterations of the redox state in this condition are caused by the chronic hyperglycemia and the increase in AGEs, which affect the renin angiotensin system and the TGF-β. This produces chronic inflammation and glomerular and tubular hypertrophy, as well as favoring the presence of OS.[4]

Reactive Oxygen Species

The ROS conform the nitrogen-centered radicals and non-radicals. The nitrogen-centered radicals include the superoxide anion, hydroxyl radical, and the peroxyl and alcoxy radicals, while the nitrogen centered non-radicals are the hydrogen peroxide, singlet oxygen, and the hypochlorous acids.[20] The increase in ROS can lead to oxidative modifications to lipids, carbohydrates, proteins, and DNA.[5,21] In DM, ROS are induced by hyperglycemia, AGEs, TGF-β, and angiotensin II.[22] The PKC, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, defects in the polyol pathways, the uncoupled nitric oxide synthase, and the mitochondrial respiratory chain oxidative phosphorylation pathway also generate ROS.[23,24] The hydrogen peroxide upregulates TGF-β1 promotes the accumulation of extracellular matrix in the mesangial cells.[25] The increase in the expression of genes of the extracellular matrix progresses to fibrosis and ESRD due to the overproduction of ROS that modulate activation of the PKC, the protein kinases activated by the mitogens, and to diverse cytokines and transcription factors.[23] The prevention of the overproduction of ROS through the control of glycemia and/or inhibition of the cytokines and growth factors, combined with the increase in the removal of the ROS preformed by conventional or catalytic antioxidants, can prevent the development and progression of DN.[26]

Reactive Nitrogen Species

The RNS conform the nitrogen-centered radicals and non-radicals. The nitrogen-centered radicals include the NO and nitrogen dioxide, while the nitrogen-centered non-radicals include the peroxynitrite, alkyl peroxynitrite, the nitroxyl anion, and nitrous acid, among others.[20] In the kidney, NO participates in the regulation of renal and glomerular hemodynamics.[27] Various clinical conditions can decrease or increase the availability of ON. In early DN, production of NO is increased. This improved production can contribute to hyperfiltration and microalbuminuria.[28] However, in advanced chronic kidney disease the severe proteinuria, the decrease in renal function, and the hypertension are associated with a progressive deficiency of NO. Factors like hyperglycemia, AGEs, and increased OS, as well as the activation of PKC and the TGF-β, contribute to diminish the production and/or availability of NO.[29] The reaction of the superoxide with NO forms peroxynitrite and decreases the bioavailability of the NO. This reduction increases vascular tone and the consumption of oxygen.[30] In DN, the kidney lesions are associated with the increase in NO and the decrease in availability of renal NO.[31] The low levels of NO in the endothelial cells can be ineffective in suppressing ROS, which leads indirectly to greater vasoconstriction. This promotes the increase in OS in the glomerular and tubulointerstitial cells.[1] Another important RNS is the peroxynitrite, which could induce the nitration of mitochondrial proteins.[32] It has been observed that the peroxynitrite plays an important role in the pathogenesis of diabetic glomerular lesions.[33]

Antioxidant Response

In response to the overproduction of ROS during respiration and metabolism, antioxidant defense mechanisms have developed.[29] The non-radical ROS are oxidizing agents that are easily converted into free radicals in physiological conditions, and the endogenous as well as the exogenous antioxidants interact with these oxidizers to counter the cellular oxidative damage. The antioxidant defense

mechanisms include the superoxide dismutase (SOD): MnSOD, and the copper-zinc-superoxide dismutase (CuZnSOD); as well as the glutathione system: GPx, and glutathione reductase, catalase, and the coenzyme Q. The antioxidant enzymes convert the ROS into molecules of non-reactive oxygen and ultimately form water. The whole antioxidant-redox system primarily uses the NADPH oxidase as a chemical reductor, which is mostly produced by the glucose-6-phosphate dehydrogenase.[18] Patients with DN type I and 2 present with alterations to the activities of the antioxidant enzymes, affecting the redox state.[35,36] The SOD is the primary defense against OS and it reacts with the superoxide to generate hydrogen peroxide, which is degraded by the catalase and GPx.[1] In experimental models, the levels of SOD are reduced in the presence of DN.[37] The utilization of SOD mimetics modified some parameters of OS such GPx, SOD, catalase y lipid peroxidation.[38,39] The therapy with Ebselen, a GPX1-mimetic, has shown to had protective effects on atherosclerosis development and DN, through the reductions of proatherogenic biomarkers and OS in DM.[40] The over-expression of catalase attenuates renal OS, prevents hypertension, albuminuria, renal hypertrophy, tubulointerstitial fibrosis and tubular apoptosis, as well as suppressing the expression of profibrotic and proapoptotic genes.[41] Ubiquinone (coenzyme Q10) has beneficial effects on the albuminuria, mitochondrial function, renal ATP production, and tubulointerstitial fibrosis in DN.[42] Activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) also plays an important role in the cellular response to OS, since it is a transcription factor with high sensitivity to OS and participates as a regulator of the expression of detoxifying enzymes, controlling the cellular antioxidant and inflammatory responses.[43,44]

DIETARY ANTIOXIDANTS ON OXIDATIVE STRESS IN DIABETIC NEPHROPATHY

Dietary antioxidants are substances in our diet that influence mechanisms of antioxidant defense by scavenging free radicals and reactive species.[45] Not only the evaluation of protein and energy should be considered at the moment of assessing these patients, but attention paid to dietary antioxidants is important because of the increase in OS that they present, and since these can act as precursors to the antioxidant enzymes, capable of diminishing the OS and preventing diabetic complications.[9,46] Recent data have demonstrated the beneficial effects of diverse dietary antioxidants on OS and the progression of DN.[47,48]

Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a phenolyic compound that is found in diverse plants and products including grapes, berries, red wine, and peanuts, with red grapes and their derivatives being the most represented dietary sources. As well, beneficial properties on cardiovascular and renal illnesses have been attributed to it. Resveratrol is a natural antioxidant that has demonstrated scavenging ROS. Its exogenous supplementation modulates the expression and activity of the antioxidant enzymes, SOD, GPx and catalase, through the transcriptional regularization of the Nrf2, the activator proteins (AP)-1, forkhead box O, and Sp1, or through enzyme modification.[49,50] Palsamy *et al.* reported in a murine model with diabetes, that the administration of oral resveratrol with a dose of 5 mg/kg/day for 30 days, normalized the renal expression of Nrf2/Keap1, the levels of creatinine clearance, and the inflammatory markers, as well as significantly improving SOD, catalase, GPx, glutathione S transferase; activities of the glutathione reductase, levels of vitamins C and E, and the reduction in glutathione levels.[51] In another recent study, the administration of resveratrol led to an increase in the levels of sirtuin 1, catalase, and activity of the SOD, as well as reducing acetylated-FOXO3a, ROS, and the levels of malondialdehyde in kidneys, which led to the lessening of OS.[52] Other beneficial effects that have been reported with the administration of resveratrol, are the attenuation of renal inflammation and mesangial proliferation, and improvement of as well as the reduction in glucose levels, creatinine, OS, proinflammatory cytokines, and up-regulating the expression and activation of the adenosine monophosphate-activated protein kinase, the latter being an important undertaking in DN.[53-55]

Curcumin

Curcumin is a phenolic compound extracted from the *curcuma longa rizoma* that is commonly used in Asia as a spice, pigment, and additive. As well, it possesses antioxidant and anti-inflammatory

functions since it participates as a bifunctional antioxidant, directly and indirectly scavenging ROS and inducing an antioxidant response. The renoprotective effect of the curcumin is associated with preservation of the redox balance and function of the mitochondria. This effect has been attributed to the antioxidant response of the Nrf2, to the inhibition of mitochondrial dysfunction, to the attenuation of the inflammatory response, the preservation of the antioxidant enzymes, and the prevention of OS.[56] In patients with type 2 DM, the administration of 500 mg/d of curcumin for a short period of time (15-30 days) has been shown to prevent DN, since it reduces the proteinuria and activates the Nrf2 antioxidant system; suppressing the level of lipopolysaccharide and the inflammatory signaling.[57] In rats with diabetes, supplementation with curcumin decreased the albuminuria by lessening of the pathophysiological changes and of OS in the glomeruli through the signaling of Nrf2, as well as decreasing the accumulation of lipids in the kidneys through the signaling of the adenosine monophosphate-activated protein kinase.[58] Lu M *et al.* observed that the administration of curcumin for 16 weeks in diabetic mice reduced renal hypertrophy, extracellular matrix expansion and albuminuria levels.[59] The activities of the PKC-α and PKC-β1 can be inhibited by treatment with curcumin, as well as the attenuation of the TGF-β1, the connective growth factor, and extracellular matrix proteins (fibronectin and collagen IV).[60] Another observed effect is the reversal of fibrogenesis through the minimization of OS and reinstating the Wnt/β-catenin pathway.[61] Recently, in diabetic patients with proteinuria, the administration of curcumin at 320 mg/d for 8 weeks was reported to not improve the proteinuria, the glomerular filtration rate, or the lipid profiles. However, in plasma the curcumin attenuated lipid peroxidation and improved the antioxidant capacity. Effects on the activities of the antioxidant enzymes or the activation of the Nrf2 were not observed.[62]

Selenium

Selenium is an essential trace element that functions as an enzymatic cofactor with > 30 selenoproteins that participate in diverse biological functions like redox signaling, the antioxidant defense system, thyroid hormone metabolism, and the immune system. The homeostasis of selenium is controlled by kidney regulation.[63,64] The primary dietary sources of selenium include: animal foods, fish like tuna and mackerel, cereals, garlic, onion, broccoli, and Brazil nuts which contain the highest content of selenium.[65] Deficiency of selenium in diet increases TGF-β1 and hyperglycemia.[66] In addition, if histomorphological changes are observed in the renal structure.[67] Bahmani *et al.* reported in patients with DN that supplementation with selenium (200 µg/day) for 12 weeks, significantly decreased the insulin levels, homeostasis of the homeostasis model of assessment-estimated insulin resistance (HOMA-IR), and the homeostasis model of assessment-estimated B cell function (HOMA-B), as well as significantly increasing the GPx (P = 0.001) compared to the placebo control group.[68] This same research group studied the effects of this intervention on the biomarkers of inflammation and OS in these patients, observing favorable effects in the levels of matrix metalloproteinase-2 (MMP-2), plasma NO, total antioxidant capacity, and glutathione. Nevertheless, significant effects were not produced in the high-sensitivity C reactive protein, TGF-β, AGEs, serum protein carbonyl, and malondialdehyde in plasma.[69]

Soy

Soy is a vegetable-based protein that possesses a high biological value, provides all of the essential amino acids, and is comparable to the quality of milk, meat, and egg, as well as containing isoflavones like genistein, daidzein, and glycitein. The soy intake has been associated with improvements in the antioxidant state and systemic inflammation in the early and later stages of chronic kidney disease.[70] Jing *et al.* concluded in their meta-analysis that soy protein intake that contains isoflavones significantly diminished the serum creatinine, serum phosphorus, C reactive protein, and proteinuria in pre-dialysis patients.[71] Recently, in a study with DN patients, the consumption of a soy milk with added whit probiotic L plantarum A7 for 8 weeks when compared to a conventional soy milk, resulted in a significant decrease in oxidezed glutathione levels, as and increment in glutathione and the activity of the antioxidant enzymes GPx and glutathione reductase. This study concluded that the consumption of probiotic soy milk can modulate some OS markers.[72] Another beneficial

effect attributed to soy-based diets in DN is the inhibition of NO, which could reduce glomerular hyperfiltration.[73] Azadbakht *et al.* evaluated the consumption of soy protein in 14 patients with DN. In the first phase a diet was assigned that contained 0.80 g/kg/d with 70% animal protein and 30% vegetable; in the following phase a similar diet was assigned with 35% animal protein and 35% soy protein, and 30% other vegetable proteins. The consumption of soy protein significantly reduced proteinuria (-78 ± 37 mg/d vs. 42 ± 19 mg/d, $P < .001$) compared to the animal protein period.[74] In a murine model with DN, they concluded that the soy supplementation with soy β-conglycinin can delay the progression of DN through the increase in sensitivity to insulin, by the regulation of lipid metabolism, as well as improvements in the markers of renal function, and inhibition of the activity of the angiotensin converting enzyme.[75]

Catechins

The catechins are flavonoids that are found naturally in diverse foods such as tea, wine, fruits, vegetables, and chocolate; known as catechin, epicatechin, epigallocatechin, epicatechin gallate, and epigallocatechetin-3-gallate.[44,76] The catechins are considered potent antioxidant and anti-inflammatory agents due to their effects in the induction of the expression of genes mediated by elements of the antioxidant response, including the phase II detoxification enzymes and enzymatic activities.[44] The epigallocatechin-3-gallate is a potent antioxidant that scavenges ROS and is found in greater quantities in green tea.[77] In a murine model with DN, the administration of epigallocatechin-3-gallate reduced levels of glucose, creatinine and proteinuria.[78] Borges *et al.* observed that in DN patients the administration of a green tea with 800 mg of epigallocatechin-3-gallate for 12 weeks, resulted in a significant reduction of albuminuria by 41% in the group treated with green tea compared to a 2% increase in the placebo group ($P < .05$).[79] Recently, it has been concluded that epigallocatechin-3-gallate can lessen and delay the progression of DN by the suppression of OS, through inhibition of the NADPH oxidase, directly suppressing the ROS and by inhibition of the expression downstream molecules of the angiotensin II mediated pathway, directly downregulating the production of effectors for renal fibrosis.[80] As well, this catechin activates the Nrf2 pathway, inactivating expression of the Kelch-like ECH-associated protein 1 (KEAP1).[81] In another murine model with DN, it was reported that the administration for 16 weeks of the catechin lessened kidney lesion by methylglyoxal metabolite trapping, which in turn inhibited the formation of AGEs and decreased the proinflammatory cytokines (tumor necrosis factor α and interleukin 1 β).[82]

Alpha Lipoic Acid

The α-lipoic acid is a naturally occuring dithiol compound that is synthesized enzymatically in the mitochondria by the octanoic acid. Its chemical properties of reduction and oxidation (redox) make it a potent antioxidant, since it directly scavenge ROS and RNS and protects the cells from OS. The dietary sources of α-lipoic acid are muscle meats, heart, kidney and liver, while in fruits and vegetables it is found in much lower concentrations.[83,84] The OS is present in the renal cortex very early in diabetes, and the α-lipoic acid has been demonstrated to have renoprotective effects on the prevention and progression of DN, countering the antioxidant loss and lipid peroxidation, and attenuating the hyperglycemia, albuminuria, the loss of renal function, expansion of the mesangial matrix, and the development of glomerulosclerosis.[85,86] Melhem *et al.* observed that the administration of α-lipoic acid in diabetic rats was effective in the prevention of early diabetic glomerular lesion, by the reduction of albuminuria and the content of TGF-β1 in the cortical tubular cells.[87] In another murine model with diabetes, the treatment with α-lipoic acid (20 mg/kg/d) for 8 weeks decreased the blood urea nitrogen (BUN) and serum creatinine, and improved histopathological profiles by the alleviation of glomerular and mesangial cellular lesions. Also, it decreased the levels of malondialdehyde and increased activity of the SOD. Another finding of this treatment was the significant increase in mitochondrial membrane potential as well as the expression of the voltage-dependent anion channel on mitochondrial.[88] In patients with DN, the combined supplementation of α-lipoic acid (800 mg) and pyridoxine (80 mg) for 12 weeks significantly decreased albuminuria, compared to the placebo group ($p = < 0.05$), through the reduction of the OS, AGEs, and systolic arterial pressure.[89]

Coenzyme Q10

The coenzyme Q10 (CoQ-10 or ubiquinone) is a fat-soluble antioxidant that prevents the generation of free radicals and modifications in the proteins, lipids, and DNA. Its principal biochemical action is that of a cofactor in the electron transport chain in the series of redox reactions that intervene in the synthesis of adenosine triphosphate (ATP).[90] The dietary sources rich in coenzyme Q10 are meat, fish, nuts, and some oils (olive, soy, corn), with the least concentrations being found in the majority of dairy products, fruits, vegetables, and cereals.[91] Its deficiency can be a precipitating factor for DN, while its supplementation can lessen it due to its beneficial effect on albuminuria, mitochondrial function, renal ATP production, and tubulointerstitial fibrosis.[92] Persson *et al.* observed that treatment with coenzyme Q10 prevents mitochondrial functional alterations and morphology, as well as glomerular hyperfiltration and proteinuria.[93] The coenzyme Q10 has demonstrated significantly inhibiting the infiltration of leukocytes, glomerulosclerosis, and malondialdehyde levels in serum and renal content; as well as significantly increasing the activity of the antioxidant enzymes, SOD, catalase, and glutathione.[94] In another murine study with DN, supplementation with this fat-soluble antioxidant with 10 mg/kg/d was demonstrated to have renoprotective effects by lessening lipid peroxidation as well as improving renal function, suppression of the tumor necrosis factor α, myeloperoxidase activity, TGF-β, and the nitrite content in renal tissue.[95] The role that the coenzyme Q10 undertakes on mitochondrial function and OS, can favorably impact the pathogenesis of DN.[96]

Omega-3 Fatty Acids

The omega-3 polyunsaturated fatty acids are essential fatty acids that are divided into alpha-linoleic acid, eicosapentaenoic acid, and docosahexaenoic acid, which can be obtained through various dietary sources, primarily fatty fish, seafood, marine algae, fish oils, walnuts, flaxseed, canola, soy, and their oils.[97,98] Experimental studies have also reported favorable effects of supplementation with omega-3 on the prevention and progression of DN, through the reduction of ROS and mitochondrial apoptosis, by improving the expression of antioxidant enzymes (SOD, GPx, catalase), by limitation of the renal formation of AGEs and the reduction of its receptor, and through the decrease in inflammatory biomarkers and tubular lesions.[99-101] Mirhashemi *et al.* observed in patients with DN that the administration of 1000 mg/d of omega-3 fatty acids from flaxseed oil for 12 weeks, resulted in a significant decrease in serum AGEs levels (-2.3 ± 2.8 AU vs. 0.2 ± 2.5 AU, $P < .05$) and the AGEs receptor (-0.1 ± 0.3 AU, $P < .05$). On evaluating the inflammatory cytokines significant changes were not produced.[102] In another study with DN patients, this same intervention was reported to have had favorable effects on the levels of insulin, HOMA-B, quantitative insulin sensitivity check index (QUICKI), serum triglycerides, and VLDL cholesterol. However, changes were not observed in the markers of inflammation and OS.[103] Lastly, the treatment with omega-3 fatty acids in diabetic patients for the management of hypertriglyceridemia has demonstrated to reduce albuminuria and maintain renal function, as well as decrease reactants like the C reactive protein, with the advantage of lessening the progression of DN.[98]

Zinc

Zinc is an essential trace element that acts as a cofactor in > 300 catalytic enzymes, and is required for the structural and functional integrity in more than 2000 transcription factors. It participates in numerous physiological functions among those that highlight its activity as an antioxidant, and as part of other proteins related to the antioxidants such as the metallothionein and the CuZnSOD.[104] Dietary sources rich in zinc include: lamb, leafy and root vegetables, kidney, liver, whole grains, pork, poultry, milk, low-fat cheese, yogurt, egg, and nuts.[105] Zinc deficiency in the diet has important repercussions on the pathogenic mechanisms involved in renal interstitial fibrosis that contribute to the development of DN; since its deficiency increases albuminuria and expression of the mesangial matrix protein, through the activation of renal interstitial fibroblasts, and by regulation of the factors of expression related to fibrosis that can be mediated by the activation of fibroblasts through the TGFβ/Smad signaling pathway.[106] Meanwhile, its supplementation has protective effects against DN through the increase in zinc concentrations as much as metallothionein,

and by the reduction of lipid peroxidation levels in the renal tissue, stimulating the synthesis of metallothionein and regulating the OS.[107] In type 2 DN patients it has been observed that treatment with zinc sulphate (50 mg/d) for 12 weeks improves the efficacy of the hypoglycemic agents, and can be beneficial in decreasing glucose, triglycerides, albuminuria, and inflammation.[108] Zinc also plays an important role on the Nrf2 in DN, since zinc deficiency is associated with a decrease in its transcription and expression, exacerbating the oxidative renal damage, inflammation, and fibrosis.[109] Other experimental studies have reported the increase in antioxidant activity through the Nrf2, NAD(P)H quinone oxidoreductase-1, SOD1, SOD2, hemeoxygenase-1, and glutamate cysteine ligase with zinc supplementation.[110,111]

Vitamin E

Vitamin E is a fat-soluble vitamin with antioxidant properties that exists in eight different forms: alpha, beta, gamma, and delta tocopherol; and alpha, beta, gamma, and delta tocotrienol, with the alpha-tocopherol being the most active form in human beings.[112] The primary dietary sources of vitamin E are the seed oils such as wheat germ oil, almond oil, and olive oil.[113] In murine models with diabetes, the administration of vitamin E has demonstrated beneficial effects on the antioxidant defense system and lipid peroxidation, increasing levels of GPx, catalase, SOD, glutathione, vitamin A, and beta-carotenes, as well as decreasing the levels of malondialdehyde in kidney.[114,115] Other beneficial effects of supplementation with vitamin E on the progression of DN is that it can decrease levels of diacylglycerol like PKC in the diabetic glomeruli. The lessening of PKC activation by administering this vitamin seems to induce normalization of the renal functions as measured by renal hemodynamics and the albumin excretion rate in urine.[116] Likewise, it has been observed that treatment with vitamin E prevents damage to the normal morphology of the podocyte and the loss of podocytes in mice without α diacylglycerol deficiency, compared to mice with deficiency of α diacylglycerol.[117] Recently, Khatami *et al.* evaluated the effects of supplementation with high doses of vitamin E (1200 UI) for 12 weeks in DN patients, finding a decrease in the levels of proteinuria, tumor necrosis factor α, matrix metalloproteinase, matrix metalloproteinase-9, malondialdehyde, AGEs, and insulin concentrations. These results show the favorable effects of this fat-soluble vitamin on the biomarkers of renal injury, inflammation, and OS in these patients.[118]

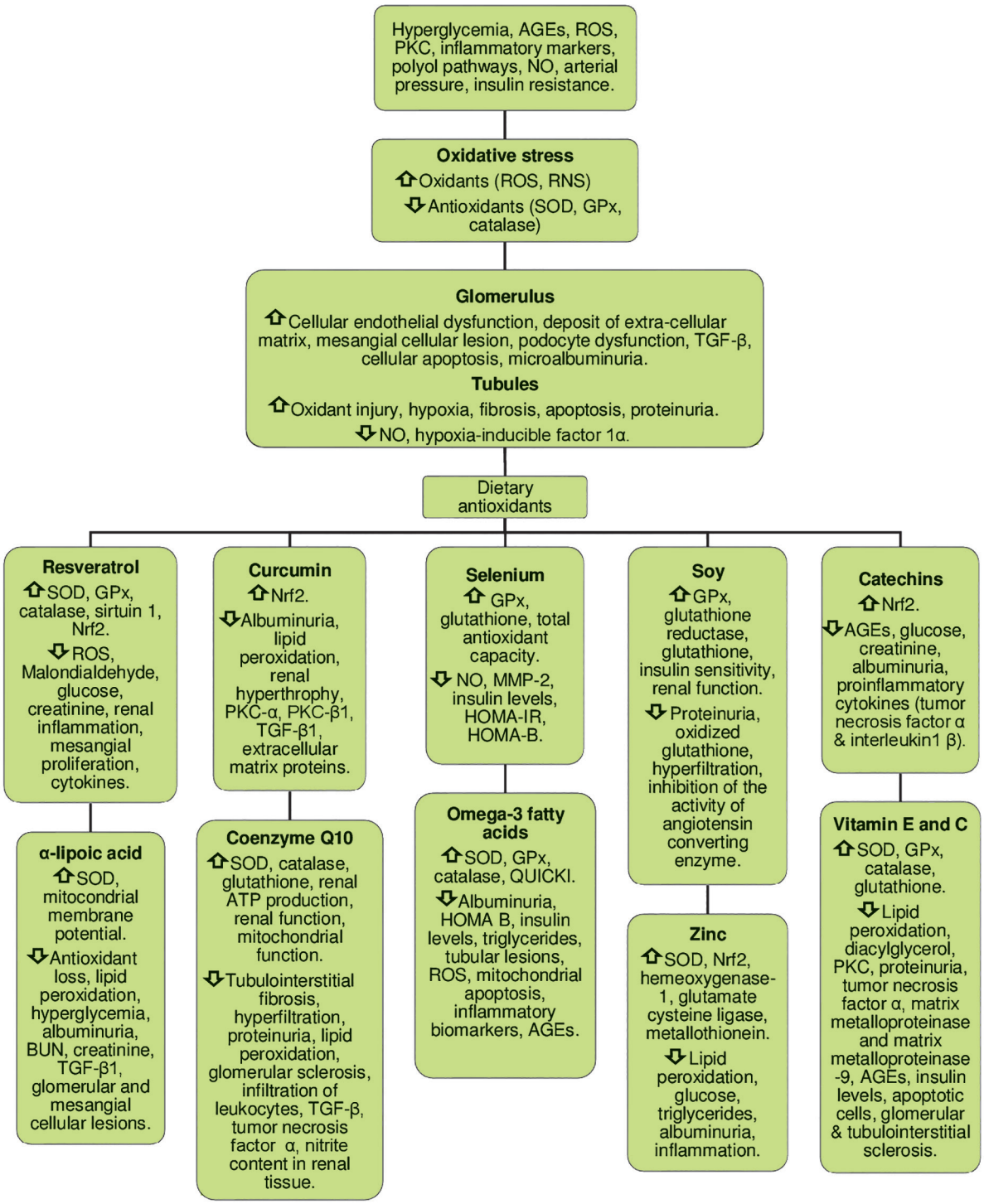
Vitamin C

Vitamin C (ascorbic acid) is a water-soluble antioxidant that prevents oxidative damage by scavenging ROS and RNS. As well, it has demonstrated anti-apoptotic activities through the maintenance of mitochondrial membrane potential and by the protection of mitochondrial DNA from the oxidant assaults. The dietary sources of this vitamin include citrus fruits and some green vegetables such as broccoli and spinach.[119] Reduced concentrations of vitamin C have been observed in patients with DN.[120,121] Factors like the increase in levels of OS, serum creatinine, albumin in urine, and the creatinine-albumin reaction in urine, have been associated with low plasma concentrations.[122] The exclusion of vitamin C from the tubular epithelial cells through the competition of glucose and dehydroascorbate, deprives the cells of the antioxidant capacity and can lead to the accumulation of ROS in diabetes.[123] The deficiency of this vitamin activates the signaling of TGF-β, aggravating the diabetic mesangial cellular expansion and the depositing of extracellular matrix.[124] Lee *et al.* reported in diabetic rats, that the treatment with vitamin C significantly reduced proteinuria, albuminuria, the number of apoptotic cells, glomerular and tubulointerstitial sclerosis, and the accumulation of renal malondialdehyde.[125] In another study, supplementation with vitamin C decreased the lipid peroxidation and increased activity of the antioxidant enzymes, SOD, GPx, and catalase, as well as reducing the albuminuria and glomerular basement membrane thickness.[126] Another beneficial effect of vitamin C, is the improvement in conditions of DN, since it diminishes the uric nitrogen in blood, serum creatinine, and the excretion rate of albumin in urine, as well as increasing the creatinine clearance rate and protecting from renal lesions by through inhibition of the expression of collagen type IV.[127] In patients with type 2 diabetes with micro/macroalbuminuria, the treatment with vitamin C and E (1250 mg of vitamin C and 680 IU of vitamin E) for 4 weeks showed a significant reduction in

albuminuria.[128] Lastly, oral supplementation with vitamin C combined with metformin has been shown to decrease glucose levels and improve the glycated hemoglobin in patients with type 2 diabetes.[129]

CONCLUSION

Factors like hyperglycemia, ROS, AGEs, arterial pressure, insulin resistance, decrease in NO, inflammatory markers, and cytokines, among others, are involved in the presence of OS on DN. The



It shows oxidative stress and dietary antioxidants in diabetic nephropathy.

Table 2. Antioxidants and Their Main Dietary Sources

Antioxidant	Main Dietary Sources
Resveratrol	Red grapes, Berries, Red Wine, and Peanuts
Curcumin	*Curcuma Longa Rizoma*
Selenium	Brazil Nut, Animal Foods, Fish (Tuna, Mackerel), Cereals, Garlic, Onion, and Broccoli
Soy	Soy Foods
Catechins	Green Tea, Wine, Fruits, Vegetables, and Chocolate
α-Lipoic Acid	Muscle Meats, Heart, Kidney, and Liver
Coenzyme Q10	Meat, Fish, Nuts, and Oils (Olive, Soy, Corn)
Omega-3 Fatty Acids	Fatty Fish, Seafood, Marine Algae, Fish Oils, Walnuts, Flaxseed, Canola, Soy, and Their Oils
Zinc	Lamb, Leafy and Root Vegetables, Kidney, Liver, Whole Grains, Pork, Poultry, Milk, Low-fat Cheese, Yogurt, Egg, and Nuts
Vitamin E	Seed Oils (Wheat Germ, Almond, Olive)
Vitamin C	Citrus Fruits and Some Vegetables (Broccoli, Spinach)

appearance of OS in this condition contributes to the pathogenesis and progression of the DN. This review has demonstrated the beneficial effects of diverse dietary antioxidants on decreasing lipid peroxidation, ROS, AGEs, hyperglycemia, insulin levels, kidney lesions, accumulation of extracellular matrix, PKC, TGF-β, and proinflammatory cytokines; as well as, the increase in antioxidant response by the SOD, GPx, catalase, glutathione, and the Nrf2 (Figure). The dietary antioxidants (Table 2) could be useful as therapeutic interventions to modulate OS, which would have favorable impacts on the pathogenesis and progression of DN.

CONFLICT OF INTEREST

There are no conflicts of interest in the writing of this manuscript.

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