Review

Oxidative Stress in Chronic Kidney Disease

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Patients with chronic kidney disease (CKD) have high incidence rates of cardiovascular disease and malignancy. Several factors contribute to these conditions. Structural characteristics in CKD, loss of renal energy, and uremia result in an imbalance between free radical production and antioxidant defenses. Also, CKD patients usually have multiple cardiovascular risk factors like diabetes mellitus, dyslipidemia, and hypertension. These conditions are associated with oxidative stress, which can trigger the inflammatory process and accelerate renal injury progression. There are some clinical biomarkers to detect oxidative stress and antioxidant status in CKD patients. Antioxidant therapies may be beneficial in reducing oxidative stress, lowering uremic cardiovascular toxicity, and improving survival. Therefore, their roles in CKD patients have been evaluated in several studies as a new target for therapeutic intervention. This review provides an overview of oxidative stress mechanisms, clinical squeals, biomarkers, and possible antioxidant therapies in CKD patients.

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INTRODUCTION

The reported annual mortality in patients with end-stage renal disease (ESRD) is about 10- to 20-fold higher than that in the general population.[1] In patients with stage 3 to 4 of chronic kidney disease (CKD), cardiovascular disease (CVD) is the leading cause of death, rather than progress to ESRD. These patients show a high cardiovascular morbidity and mortality as a result of endothelial dysfunction and left ventricular hypertrophy that could be triggered by oxidative stress and inflammation. There are several risk factors for developing cardiovascular disease in CKD patients that could be separated into traditional and nontraditional risk factors. Diabetes mellitus, older age, hypertension, and hyperlipidemia are traditional risk factors commonly present in the CKD population.[2] Atherosclerosis and CVD in CKD patients are associated with oxidative stress, inflammation, and reduced nitric oxide availability.[3] Oxidative stress and inflammation are considered nontraditional risk factors.[4]

There are also some renal-specific risk factors like uremia and dialysis that could lead to changes in serum cytokines and eventually carotid artery intima-media thickness (CIMT) of and left ventricular hypertrophy.[2] Oxidative stress as a consequence of increase in reactive oxygen species (ROS) and decrease in antioxidant defenses is prevalent in many health problems like CKD and it still exists after transplantation.[5] Oxidative compounds have physiologic defense mechanisms in the body, but imbalance in oxidant generation results in tissue damage. Oxidative stress induces endothelial dysfunction and progression of atherosclerosis by reducing nitric oxide availability.[6]

REACTIVE OXYGEN SPECIES

Exposure to stimuli causes activation of phagocyte oxidant generation system and leads to increased oxygen consumption. Reactive oxygen species are generated through several main enzymatic processes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which reduces oxygen

to superoxide anion (O_2^-); this anion is converted into hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD). Superoxide anion (O_2^-) reacts with nitric oxide, which produces peroxynitrite (nitrosative stress). Hydrogen peroxide reacts with intracellular iron to form hydroxyl radical. Also, H_2O_2 is catalyzed to hypochlorous acid in the presence of chloride ion, by myeloperoxidase activity. In addition, cytokines are released from activated monocytes. Uremic toxin can also increase ROS generation. Excessive reactive ROS can lead to oxidation of lipid, proteins, and DNA.[7]

OXIDATIVE STRESS AND CHRONIC KIDNEY DISEASE

Mitochondria are involved in several metabolic pathways such as calcium and iron homeostasis, ROS production, and apoptosis. Impaired mitochondrial respiratory system in CKD patients is suggested both as the consequence and the cause of an enhanced oxidative stress, which may explain a subnormal energy metabolism in this population. Reactive oxygen species can influence cell function and damage proteins, lipids, and nucleic acids, and also can inhibit enzymatic activities of the cellular respiratory chairs. Progression of CKD to advanced stages is associated with a significant increase in the generation of ROS. Renal replacement therapy can be beneficial in improving some biochemical alteration of end-stage disease, but partially treated uremia, fluctuation in the extracellular fluid volume, and exposure to bioincompatible dialysis devices cause increased synthesis and release of proinflammatory cytokines and high oxidative stress and immune system dysregulation.[8]

Genetic polymorphism in antioxidant enzyme glutathione S-transferases could contribute to some level of oxidative agent production and cardiovascular prognosis in ESRD patients.[9]

Kidney transplantation ameliorates oxidative status of chronic uremic state, evident by increased glutathione and decrease in advanced oxidation protein products (AOPP), thiobarbituric acid reactive substances (TBARS), and total antioxidant capacity, without change in antioxidant enzyme activities (glutathione peroxidase [GP], catalase, and SOD) during 6 months posttransplantation period.[10]

Changes in oxidative and antioxidant status, which occur from the early stages of CKD, could be exacerbated by hemodialysis.[11] Removing antioxidant substances via the dialysis, hemoincompatibility of the dialysis system,[12] and trace amounts of endotoxins in the dialysate are possible factors responsible for pro-oxidant status in hemodialysis patients, which trigger NADPH oxidase activation and ROS overproduction. Long-term sequel of this state could accelerate atherosclerosis, amyloidosis, anemia, and malnutrition.[13]

In several studies, diabetes mellitus, older age, hypertension, and hypoalbuminemia have been introduced as predictors of ischemic heart disease in patients on hemodialysis, but the high prevalence of cardiovascular morbidity and mortality could not be explained enough by classic cardiac risk factors in these populations; thus, it is possible that some other etiologies like oxidative stress, endothelial dysfunction, and hyperhomocysteinemia contribute to detrimental effects of these conditions.[14] Use of biocompatible membrane, ultrapure dialysate, and antioxidant vitamins, and extracorporeal removal of ROS and oxidatively-modified substances could be beneficial in prevention of long-term complication in these patients.[12] In hemodialysis patients, activation of phagocyte system contributes to ROS generation,[15] which can damage leukocyte DNA.[16]

Oxidative stress is associated with impaired endothelium-derived nitric oxide activity, which is the early mechanism in the development of atherosclerosis. Long-standing oxidative stress and low-grade inflammation in ESRD patients associated with CIMT, which is the marker for early stage of atherosclerosis.

Intravenous iron therapy in hemodialysis patients, even in recommended doses, could aggravate oxidative stress and atherosclerotic disease in this population. Furthermore, increased total body iron level exacerbates lycopene and other lipophilic antioxidants deficiency,[17] while in the absence of concomitant iron supplementation, erythropoietin therapy does not affect oxidative stress, coagulation activation, and endothelial injury markers in hemodialysis patients.[18]

Duration of hemodialysis can influence oxidative damage, which is proven by an increase in malondialdehyde level, but it has no effect on protein carbonyl levels. Total sulfhydryl levels and SOD activity are decreased significantly in

longer hemodialysis periods.[19] In diabetic patients, hemodialysis was associated with higher levels of oxidized low-density lipoprotein cholesterol (LDLC), plasma TBARS, and protein carbonyl, but lower plasma thiol levels as compared to peritoneal dialysis (PD).[20] However, Filiopoulos and colleagues reported similar degrees of inflammation and oxidative stress status in hemodialysis and PD patients.[21] Similar results were observed in another study in patients undergoing regular dialysis treatment; serum total antioxidant status and adjusted coenzyme Q10 levels are decreased and total oxidant status are increased both in hemodialysis and PD without significant difference.[22] Total plasma thiol levels, an indicator of antioxidant capacity, improves after kidney transplantation compared to pretransplant levels.[23] However, Kuchta and colleagues showed that the uremia state rather than dialysis treatment contribute to oxidative stress in both dialyzed and nondialyzed patients.[24]

In a prospective cohort study, initiation of maintenance hemodialysis did cause a significant change in carbonyl content levels as oxidative stress marker and inflammatory markers in uremic patients.[25] A single-session hemodialysis can decrease levels of some oxidative stress markers like total oxidant status, oxidative stress index, and antioxidants such as total antioxidant status and arylesterase; as a result, hemodialysis did not increase oxidants but caused reduction in antioxidant reserve.[26]

Zanetti and colleagues reported that p66 (shc) gene expression, which stimulates oxidative stress and atherogenesis, was increased in hemodialysis patients incorrelation with tumor necrosis factor-α mRNA and oxidative stress markers.[27]

DIABETES AND OXIDATIVE STRESS

One of the major causes of ESRD is diabetic nephropathy. Oxidative stress and changes in cellular function play a key role in the development and progression of diabetic nephropathy. As angiotensin II can produce ROS via NADPH oxidase, rennin-angiotensin system blockade could decrease ROS generation and reduce the rate of kidney disease progression in these patients. But progression still persists, as more than one source of ROS generation exists in diabetic nephropathy, such as mitochondria, which explain the importance of identifying new therapeutic targets in preventing progression of kidney damage.[28] Advanced glycation end products (AGEs), NADPH oxidase, defects in polyol pathway, uncoupled nitric oxide synthase, and mitochondrial respiratory chain (via oxidative phosphorylation) contribute to ROS generation.[29] Advanced glycation end products are formed via glucose interaction with proteins, lipids, and nucleic acids. As kidney is the major site of AGE clearance, both chronic hyperglycemia and impaired kidney function contribute to AGE accumulation in diabetic patients. Advanced glycation end products may exert deleterious effects such as alteration of vascular structure and function and enhanced oxidative stress and inflammation. The kidney could be a target for AGE-mediated damage. Oxidative stress also promotes the formation of AGEs, independently of glucose levels.[30]

DYSLIPIDEMIA AND OXIDATIVE STRESS

Chronic kidney failure results in dysregulation of lipid metabolism, especially high-density lipoprotein cholesterol (HDLC) and triglyceride-rich lipoproteins, which contributes to arteriosclerotic cardiovascular disease and possibly accelerated progression of kidney disease. Several animal and clinical studies demonstrated the role of hyperlipidemia in kidney disease progression. The potential role of statin therapy in deliberating kidney function decline by both lipid-lowering and anti-inflammatory effects are assessed in some studies.[31] Oxidative stress as a potentially important mechanism of atherosclerosis already presents at the earlier stages of CKD.[32]

Presence of AOPPs which are considered as potential uremic toxins and inflammatory mediators, lead to phagocyte activation and atherosclerosis in hemodialysis patients.[15] The positive correlation of copper/zinc SOD levels with endothelial injury markers in hyperlipidemia suggests the role of oxidative stress as an etiologic factor in vascular dysfunction and atherosclerosis in hemodialysis patients.[33]

INFLAMMATION AND OXIDATIVE STRESS

Markers of inflammation (interleukin-6, tumor necrosis factor-α, and C-reactive protein [CRP]) and oxidative stress (plasma protein carbonyls and F2-isoprostanes) are elevated in ESRD patients, but

reduction of their levels are observed after kidney transplantation which persists for 2 months.[34]

Lower glutathione in CKD patients was associated with poor endothelium-dependent vasodilation.[35] In a cohort study, patients with CVD had higher plasma interleukin-6 and CRP levels, among whom patients on statin showed lower levels of interleukin-6; patients taking angiotensin II inhibitors had lower CRP levels. All the CKD patients had increased levels of oxidative stress, especially diabetic and hypercholesterolemic patients. These results emphasize the role of inflammation and oxidative stress on cardiovascular event in CKD patients.[36] In a study by Pupim and colleagues, CRP, interleukin-6, and carbonyl content levels were significantly higher in hemodialysis patients than healthy subjects.[25] Short-term administration of simvastatin significantly reduced LDLC and total cholesterol but could not reduce inflammatory and oxidative stress markers in patients with stage 3 and 4 CKD.[37]

BIOMARKERS

Overview

Oxidants are highly reactive compounds with a half-life of only seconds; therefore, evaluation of oxidative stress by using them as biomarkers of oxidative stress in clinical setting is difficult. In contrast, measurement of stable markers with long half-lives such as molecules (lipids, proteins, carbohydrate, and DNA) modified by interaction with ROS and enzymatic and nonenzymatic antioxidants that change in response to oxidative state could be helpful.[38]

Some of these biomarkers were well-suited in a systematic review in CKD population such as malondialdehyde, lipid hydroperoxides, F2-isoprostanes, asymmetric dimethyl arginine (ADMA), protein carbonyls, AOPPs, 8-oxo-7,8-dihydro-2′-deoxyguanosine,and glutathione-related activity. Isofurans and cholesteryl esters still need more research as novel biomarkers.[39]

Lipid Peroxidation

Molecular structure of lipids makes them susceptible to oxidation; acrolein, malondialdehyde, 4-hydroxynonenal, and TBARS are produced during lipid peroxidation.[38] Peroxidation of membrane polyunsaturated fatty acids by free radicals produces some molecules such as malondialdehyde that could be useful as an indicator for assessing oxidative damage. Significant elevation of serum malondialdehyde levels in CKD and hemodialysis patients with CVD, compared with those without CVD,[40-42] shows the relationship between oxidative stress and the development of atherosclerosis in these patients.[43] Although the increase in malondialdehyde level after hemodialysis is reported in some studies,[42,44,45] malondialdehyde is a water-soluble low-molecular-weight product of lipid peroxidation, and it could be removed by hemodialysis; therefore, its value as a marker of oxidative stress during hemodialysis is limited. In contrast, lipid hydroperoxide, which is another product of lipid peroxidation, is lipid-soluble and difficult to remove by hemodialysis; therefore, it is a more reliable biomarker of oxidative stress in ESRD patients.[46,47]

Enzymatic or nonenzymatic LDLC oxidation plays a role in atherosclerosis pathogenesis and could be detected by using specific monoclonal antibodies.[48] Elevated lipid peroxides and LDLC oxidation levels are reported in ESRD patients prior to the start of renal replacement therapy.[49] Also, lipid peroxide levels and autoantibodies against oxidized LDLC are increased after hemodialysis, which could explain the role of increased oxidative stress in accelerated atherosclerosis of CKD patient.[33]

Thiobarbituric acid reactive substances assay is a nonspecific marker of lipid peroxidation.[39] Thiobarbituric acid reactive substances and reactive carbonyl derivates levels were higher both in serum and urine of patients with diabetic nephropathy.[50] In a cross-sectional study, reduction in plasma TBARS levels were observed after a single hemodialysis session.[27] In PD patients, serum TBARS levels were significantly higher than healthy individuals.[51]

Plasma levels of oxysterols were higher in hemodialysis patients, but there were no association between this oxidative stress marker and inflammation, nutrition, and CVD in this population.[23]

Arachidonic Acid-derived Oxidation

F2-isoprostanes are formed by nonenzymatic oxidation of arachidonic acid, a polyunsaturated fatty acid present in phospholipids of cell membrans,[38] and could be detected in serum and urine samples.[48] Increases in lipid peroxidation in ESRD patients cause an increase in plasma

levels of 8-iso-prostaglandin F2α, especially in patients on hemodialysis rather than PD, which had a linear correlation with serum haptoglobin, CRP, and plasma malondialdehyde, and an inverse association with serum albumin and total cholesterol. The relationship between this biomarker and acute-phase reactant proteins indicates the link between lipid peroxidation, inflammation, and atherosclerosis in ESRD patients.[52]As renal clearance and hemodialysis could alter plasma levels of free isoprostanes, the esterified F2-isoprostanes would be a more reliable marker of oxidative stress in this clinical setting.[53]

Protein Oxidation

Tyrosine nitration has been used as an oxidative stress indicator, which is associated with coronary artery disease.[48] Myeloperoxidase is an enzyme that contributes to ROS generation and is associated with increased coronary artery disease risk.[48] Increase in Serum myeloperoxidase and nitrotyrosine and decrease in total antioxidant capacity in hemodialysis patients indicate oxidative stress procedures in this population.[54]

Advanced oxidation protein products and AGEs are markers of protein oxidation.[38] Chlorinated oxidants, which are generated by myeloperoxidase, are important in the formation of AOPPs.[55] Advanced oxidation protein products are considered markers of oxidant-mediated protein damage and proinflammatory mediators. These markers accumulate in CKD, especially hemodialysis patients, and they are an independent risk factor for ischemic heart disease in this population.[56] Furthermore, AOPPs mediate monocyte activation associated with chronic uremia and contribute in uremia-associated immune dysregulation.[57] Advanced oxidation protein products levels have a positive correlation with serum malondialdehyde levels, while a negative correlation with glutathione peroxidase is reported. Also, high serum AOPPs levels are reported in patients with carotid artery plaques. Strong association of AOPP serum levels and CIMT and CRP indicates the role of AOPP in inflammation and pathogenesis of atherosclerosis by phagocyte-induced inflammation.[17,58] Zhou and coworkers reported that triglycerides and other endogenous factors cause overestimation of AOPPs in CKD patients.[56]

Advanced glycation end products are carbohydrate-derived compounds which are formed nonenzymatically as a result of oxidative stress-induced carbonyl stress (increase in carbonyl group formation) and act as the marker of protein glycation. Its biological activity mediated via the receptor for advanced glycation end products causes stimulation of nuclear factor kappa B in hemodialysis patients.[59] Formation of AGEs is increased in CKD patients, independent of diabetes mellitus or aging. Plasma AGE pentosidine correlates with plasma AOPPs levels, which suggests the relevance of AOPPs and AGEs in monocyte-mediated inflammatory syndrome associated with uremia.[57]

Protein carbonyls are formed by oxidation of amino acid residues on proteins and are used as a marker of oxidative modification of proteins, high levels of which are reported in several diseases such as CKD.[60] Increased protein carbonyl content in CKD as a marker of carbonyl stress correlates with CRP and fibrinogen; it reduces significantly after kidney transplantation.[23] By kidney failure progression, plasma protein, mainly albumin carbonyalation, is increased and intensified during hemodialysis, but not in PD.[61] In a cohort of 60 patients with stage 3 to 5 CKD, increased levels of plasma protein carbonyl group, plasma free F2-isoprostane, and plasma protein reduced thiol content, were reported compared to healthy individuals.[36]

Nucleic Acid Oxidation

The marker of leukocyte DNA damage, 8-hydroxy-2′-deoxyguanosine, is increased as a result of interaction between oxidative compounds with nucleic acids.[38] 8-hydroxy-2′-deoxyguanosine levels gradually increased with progression of kidney failure and could be exacerbated by PD.[62] A profound increase in 8-hydroxy-2′-deoxyguanosine levels was seen in hemodialysis patients using a complement-activating dialysis membrane (cellulose membranes), while decreased after switching to synthetic membranes (polymethylmethacrylate or polysulfone).[16] The negative correlation between plasma oxidative DNA damage and endothelial function[42] and the positive correlation between CIMT and the ratio of 8-hydroxy-2′-deoxyguanosine to deoxyguanosine in hemodialysis patients show that the ratio of 8-hydroxy-2′-deoxyguanosine to deoxyguanosine could be informative in risk

determination of accelerated atherosclerosis in this patient population.[45]

Antioxidants

Endogenous enzymatic and nonenzymatic antioxidant mechanisms contract with damaging effects of oxidative products. Vitamin E, β-carotene, and coenzyme Q are fat-soluble antioxidants existing in cellular membrane. Water-soluble antioxidants include vitamin C, glutathione peroxidase (glutathione -Px), SOD, and catalyse. Ferritin, transferrin and albumin exert anon-enzymatic antioxidant effect by sequestering transition of metal ions.[6]

Total antioxidant status is assessed by different measurement techniques make it difficult to interpret in CKD patients.[39] Reduction in the antioxidant defense capacity measured by total antioxidant capacity and thiol concentration, also by increase in pro-oxidant capacity in the serum of hemodialysis patients.[63] Total antioxidant capacity and SOD were significantly lower in hemodialysis and PD compared to healthy controls.[21] While a questionable role of total antioxidant capacity as a marker for assessing oxidative stress in CKD patients is reported by Bergesio and colleagues.[64]

Enzymatic Antioxidants

The first line of enzymatic anti-oxidant defense is SOD, which accelerates the dismutation rate of oxygen to H_2O_2 but catalase reduces H_2O_2 to water. Glutathione peroxidase reduces H_2O_2 and other organic peroxides to water and oxygen, and requires glutathione as a hydrogen donor which is a scavenger for H_2O_2, hydroxyl radical and chlorinated oxidants.[6] Decreased total level of glutathione and plasma GP activity are reported in CKD patients.[11]

Evaluation the activity and status of enzymatic antioxidants such as GP, catalase, and SOD are also used to assess oxidative stress in CKD patients. Renal tubules are the prominent site of GP synthesis, and in hemodialysis patients, GP activity is reduced to half, as a result of active nephron mass reduction.[65] Lower glutathione levels and reduced activities of GP and glutathione reductase are reported in CKD patients simultaneously with elevation in SOD, glutathione transferase and catalase activities.[41] In hemodialysis patients, decreased SOD and GP activity are observed in comparison to healthy controls.[42] In uremic patients, GP and reductase activity of erythrocytes were increased at the early stage of CKD, while plasma GP activity and total level of glutathione were decreased.[11] A decrease in plasma but not erythrocyte GP activity is associated with progression of CKD; hemodialysis can increase plasma GP activity while erythrocyte GP activity does not change significantly after dialysis.[66] In a study by Annuk and associates, oxidized glutathione level in plasma and glutathione redox ratio were considered the most informative indexes of oxidative stress status in CKD patients, while erythrocyte GP activity has an inverse association with cardiovascular events.[48,67]

Plasma copper/zinc SOD level is a simple and sensitive biomarker for oxidative stress in ESRD population,[68] but results are contradictory and difficult to interpret, as in some studies copper/zinc SOD levels are increased in CKD,[69] and hemodialysis patients relative to controls, and hemodialysis patients showed higher levels in comparison to PD group;[33] While in other studies, SOD and GP activities are decreased and negatively correlated with CIMT in hemodialysis patients.[45] On the other hand, in a study by Atamer and coworkers no significant differences were reported in the SOD and catalase activities between CKD patients and the control group.[40] Findings related to catalase activity are inconsistent in CKD patients, but it could be a more reliable marker for antioxidant status in diabetic patients.[39]

Paraoxonase/arylesterase, also known as aromatic esterase 1 or serum aryl dialkyl phosphatase 1, is an enzyme that is encoded by the paraoxonase 1 gene in humans. Paraoxonase 1 has esterase and more specifically paraoxonase activity. It has a protective effect against lipoprotein oxidation and is a sensitive antioxidant status marker, but limited data is available about it.[39] Reduction in paraoxonase activity was reported in CKD patients which correlated with levels of homocysteine, malondialdehyde, HDLC, lipoprotein a, and apolipoprotein A-I.[40] Johnson-Davis and colleagues demonstrated that the decrease in antioxidant activity such as paraoxonase and glutathione peroxidase correlated with increase in oxidative stress measured by F2-isoprostanes, selenium, and oxidized LDLC concentrations.[70]

Gamma glutamyl transferase, an enzyme which plays a major role in the extracellular catabolism

of glutathione, has a high predictive value for all-cause and cardiovascular mortality in ESRD patients, which could suggest its role in oxidative stress mechanisms.[71]

Nonenzymatic Antioxidants

Reduced glutathione is a major nonenzymatic cellular antioxidant which is dependent on GP activity. As GP activity is reduced in hemodialysis patients, elevation in erythrocyte glutathione is not enough to protect against oxidative damage.[65] Measuring glutathione in erythrocytes showed contradictory results, while reduction of glutathione concentration is reported in whole blood.[72]

Decreased in glutathione levels are reported in CKD patients and has a negative correlation with uremic toxins nevertheless positive correlation exist between glutathione and creatinine clearance. In comparison with SOD, it is a stable indicator with less fluctuation.[39]

Lycopene is a carotenoid, an effective exogenous antioxidant which protects critical biomolecules including lipids, LDLC, proteins, and DNA. Reduced lycopene levels and GP enzyme activity in hemodialysis patients are associated with lipid peroxidation. A negative relationship of lycopene levels with malondialdehyde levels, LDLC, and the LDLC/HDLC index was observed in one study.[65]

Lim and colleagues suggested lipophilic antioxidants as markers of oxidative stress in ESRD patients undergoing hemodialysis, as lower plasma levels of lycopene, delta-tocopherol, gamma-tocopherol, and retinol are reported in these subjects compared with the control group.[73]

Deficiency of vitamin C, an abundant nonenzymatic antioxidant, is prevalent in hemodialysis as a result of dietary restriction or removal during dialysis,[74] and it predicts adverse cardiovascular outcomes in this patient population.[75] Also, plasma vitamin E levels are decreased significantly in CKD patients compared to healthy individuals.[76]

Hydrogen Sulfide

Hydrogen sulfide is an endogenous signaling gas with antioxidant, anti-inflammatory, and antihypertensive activity; its deficiency can potentially contribute to CKD progression. In an animal study by Aminzadeh and coworkers, reduced plasma concentration of hydrogen sulfide and hydrogen sulfide-producing capacity of the kidney and liver were reported.[77]

Glutathionyl Hemoglobin

Product of hemoglobin S-glutathionylation is considered as an oxidative stress marker.[48] Oxidized glutathione disulfide is a source of glutathionyl hemoglobin and the oxidized glutathione disulfide to reduced glutathione ratio is increased in uremia. Oxidative stress induces increase in glutathionyl hemoglobin levels in patients undergoing dialysis, which indicates its role in assessing oxidative status in these patients.[78]

Asymmetric Dimethyl Arginine

The decrease in nitric oxide production in CKD patients could be a result of L-arginine deficiency (substrate) or increased ADMA level, which contributes to cardiovascular events and CKD progression. Asymmetric dimethyl arginine, as a major independent risk factor in ESRD,[79] inhibits endothelial nitric oxide synthase and increases superoxide production of endothelium.[39] It is an important stress marker in CKD patients, whose levels is increased in patient undergoing hemodialysis and PD and independently predict the CIMT.[51,80] Reduced renal excretion and reduced catabolism by dimethyl arginine dimethyl aminohydrolase contribute to increase plasma and tissue levels of ADMA in these patients.[79]

Kynurenine Pathway

Degradation of tryptophan, the essential amino acid, produces kynurenine. Its metabolites (kynurenic and anthranilic acid) are increased in many diseases, such as CKD,[81] reflecting increased activity of kynurenine pathway enzymes in this population.[82] Evaluating the role of kynurenine pathway in the pathogenesis of atherosclerosis showed an association of kynurenine pathway activation with increased oxidative stress,[83] inflammation,[84] and endothelial dysfunction in ESRD patients.[81]

Among all biomarkers mentioned before, there are some markers that measuring them is practical and recommended for assessing the oxidative stress level in ESRD patient, such as glutathione, the glutathione redox ratio, intracellular enzymatic antioxidants such as SOD and GP and also markers of LDLC oxidation and AOPP.[85]

TREATMENT OF ANTIOXIDANTS

Vitamin C and Vitamin E

Vitamin E protects the cell membrane from lipid peroxidation by forming a low-reactivity tocopheroxyl radical, and vitamin C directly scavenges O_2^- and hydroxyl radical. Alpha and gamma tocopherol, the major components of vitamin E, have antioxidant capacity. In an animal study, antioxidant supplementation with vitamins E and C and β-carotene for 4 weeks reduced serum 8-oxo-2′-deoxyguanosine, the marker of DNA damage in cats with renal insufficiency.[86]

Long-term administration of vitamin E increased LDLC resistance to oxidation in hemodialysis patients without any significant effect on lipid profile.[87] Increased oxidation of LDLC as a result of the increase in oxidative stress could contribute to pathogenesis of atherosclerosis, and supplementation with α-tocopherol, 800 IU/d for 12 weeks, decreased the susceptibility of LDLC to oxidation in patients on dialysis specially PD.[88] It could reduce myocardial infarction in hemodialysis patients with preexisting CVD.[89]

Supplementation with catechin (a type of natural phenol and antioxidant), vitamin E, and vitamin C decreased malondialdehyde and ADMA in kidney failure patients.[90] Vitamin E, both in oral form and as coating of a dialyzer, could decrease copper/zinc SOD content levels in hemodialysis patients.[91] Vitamin E-coated polysulfone membrane exerts antioxidant activity by reducing ADMA accumulation in patients treated with hemodialysis.[92] Also long-term use of a vitamin E-coated cellulose acetate dialysis membrane suppressed biomarkers of oxidative stress and inflammation.[93]

In a study by Himmelfarb and colleagues, administration of γ-tocopherol and docosahexaenoic acid had no significant effect on plasma concentrations of CRP, F2-isoprostanes, and carbonyls in hemodialysis patients, but reduced selected inflammatory markers.[94] In other study administration of mixed tocopherols and alpha lipoic acid combination, could not change F2-isoprostanes, protein thiols, and markers of inflammation in stage 3 to 4 of CKD.[95] Lack of efficacy of this oral antioxidant therapy on selected biomarkers of acute-phase inflammation and oxidative stress was observed even in hemodialysis patients.[96]

Effects of vitamin C are assessed in some studies with contradictory results. Oral supplementation of 1000 mg of vitamin C in hemodialysis patients lead to an increase in the oxidized form of vitamin C, which shows its antioxidant effect, but plasma copper/zinc SOD or its mRNA expression in leukocytes does not change.[97] Intravenous administration of vitamin C, increased paraoxonase 1 activity and decreased AGE and lipid hydroperoxides,[98] lymphocyte 8-oxo-2′-deoxyguanosine levels, and intracellular ROS production in hemodialysis patients.[99]

Co-administration of 200 mg of vitamin C and 600 mg of vitamin E daily for 6 months in patients undergoing hemodialysis decreased lipid peroxidation marker and could be effective in improving microcirculatory disturbance by attenuating oxidative stress.[100] Also, in PD patients, combination of vitamin C and E improved all biomarkers of oxidative stress such as increased erythrocyte antioxidant enzymes activity and total antioxidant capacity levels and decreased malondialdehyde concentration and carbonyl compound formation.[101]

Whereas short-term administration of vitamin C (250 mg, 3 times per week) did not improve markers of oxidative stress and antioxidant status in hemodialysis patients,[102] 1-year administration of vitamin C, 1000 mg/d, showed a trend toward a decrease in oxidation products in hemodialysis patients, although significant differences in lipoperoxidation were not seen as compared to the control group.[103]

Omega-3 Fatty Acids

In addition to the beneficial effect on controlling hypertriglyceridemia, administration of omega-3 ameliorates oxidative stress, evident by lowering TBARS and increasing serum SOD, GP, and catalase activities in CKD patients with dyslipidemia, but carbonyl values does not change significantly.[104] Omega-3 fatty acids supplementation, 3 g/d for 2 months, reduced malondialdehyde levels and increased antioxidant status (GP and SOD) in hemodialysis patients.[105]

N-Acetylcysteine

The thiol restoration pathway could mitigate harmful effects of ROS by providing adequate scavenging capacity in CKD patients.[72] Attenuation of oxidative stress by N-acetylcysteine

administration decreased uremia-induced atherosclerosis in an animal model of chronic kidney failure.[106] Beneficial effects of N-acetylcysteine on intracellular oxidative stress and apoptosis rate of T lymphocytes in ESRD was demonstrated alone and in combination with vitamin E.[107] Concomitant administration of vitamin E and N-acetylcysteine in children undergoing dialysis reduced intracellular oxidative stress in T cells and could be effective in lowering oxidative stress-induced functional disability of lymphocytes.[108] A single dose of N-acetylcysteine lowered prehemodialysis plasma homocysteine level but did not influence postdialysis homocysteine levels.[109] An increase in hematocrit and a decrease in 8-isoprostane and oxidized LDLC in plasma of hemodialysis patients on N-acetylcysteine therapy showed the beneficial effect in management of anemia and oxidative stress.[110] On the other hand, reduced N-acetylcysteine clearance in ESRD patients limited its role as long-term therapy in reducing oxidative stress complications in these patients.[111]

Carnitine

Effect of carnitine supplementation on improving outcome of hemodialysis patients was demonstrated by reducing oxidative stress and chronic inflammation.[112] Administration of L-carnitine, 20 mg/kg intravenously, increased glutathione and GP activity and decreased malondialdehyde and protein carbonyl in hemodialysis patients.[113] Decline in plasma antioxidant capacity after hemodialysis via cellulosic membrane was attenuated by L-carnitine supplementation in another study.[114] In an animal CKD model reduced plasma antioxidant activities (SOD, catalase, and GP) decreased plasma and tissue (heart and kidney) glutathione levels and increased tissue malondialdehyde levels, all were reversed by exogenous supplementation of L-carnitine.[115]

Coenzyme Q10

Patients with CKD even on hemodialysis or PD reported to have similar serum levels of antioxidant coenzyme Q10.[116] Patients on dialysis treatment had lower coenzyme Q10-cholesterol ratio and total antioxidant status compared to controls, and coenzyme Q10 was significantly lower in PD patients than healthy individuals.[22] Sakata and associates assessed the effect of coenzyme Q10 on the plasma AOPPs, malondialdehyde, and total antioxidant capacity in hemodialysis patients and showed coenzyme Q10 administration caused suppression in both oxidative stress and antioxidant indices, so it was partially effective in lowering oxidative state.[117]

Folic Acid

Folate acts against lipoperoxidation and hyperhomocysteinemia in patients on hemodialysis and can be helpful in decreasing cardiovascular risk in this population.[118] Hyperhomocysteinemia caused reduction in endogenous hydrogen sulfide generation and renal damage. Supplemention with hydrogen sulfide in animal models showed antioxidant effects and was protective in renal damage induced by hyperhomocysteinemia.[119]

Statins

Treatment of CKD patients with the lipid-lowering agent, atorvastatin, reduced oxidized LDLC, total cholesterol, triglyceride, LDLC, and apolipoprotein B in patients on dialysis, while co-administration of atorvastatin and α-tocopherol added beneficial effects on LDLC oxides ability in vitro.[120]

Trace Elements

Selenium. Selenium is an essential trace element with antioxidant properties, which incorporates in GP as selenocysteine and plays an important role incellular protection as a free radical scavenger.[121] Decreased plasma and whole blood selenium concentration and plasma GP activity in CKD patients were reported. Selenium levels were similar in different stages of disease, while a decrease in GP activity was associated with increase in CKD stage. Selenium supplementation was ineffective on increasing GP activity in ESRD patients.[122] Lack of selenium efficacy in changing Level of GP protein in hemodialysis patients suggests that GP protein deficiency is a result of a decrease in its synthesis from damaged kidney, rather than selenium deficiency.[123] In hemodialysis patients, plasma GP activity was reported to be 44% to 60% of healthy controls.[124] Improvement of glomerular filtration rate was reported after administration of an oral supplement of sodium selenite both in CKD and normal individuals.[125] Decreased serum selenium level in CKD patients,

which contributed to compromised antioxidant system, could be as a result of protein loss and dialysis. Selenium deficiency was associated with immune system dysfunction and increased risk of death due to infection and coronary artery disease in hemodialysis patients.[126] Supplementation of selenium improved plasma and erythrocyte selenium concentration, GP activity, and erythrocyte alpha-tocopherol,[127] and also prevented DNA damage in hemodialysis patients.[128] Selenium supplementation in hemodialysis patients on erythropoietin therapy resulted in increased plasma selenium and erythrocyte GP activity, while plasma GP activity, SOD, and plasma and erythrocyte TBARS did not change.[129] In a study by Milly and colleagues, selenium concentration in plasma, serum or whole blood of dialyzed and nondialyzed CKD patients and healthy controls were similar and was not influenced by dialysis therapy; therefore, trace elements supplementation is recommended only in patients with proven deficiency.[130]

Zinc. Deficiency of zinc and magnesium were reported in sera of CKD children.[131] Zinc deficiency was more prevalent in hemodialysis than PD and was related to CRP levels and inflammatory response in hemodialysis.[132] Zinc supplementation in patients on long-term dialysis treatment increased selenium concentration and decreased oxidative stress and plasma aluminum. In addition, relation between increased zinc concentration and level of selenium, aluminum, malondialdehyde, and SOD activity was observed.[133] Hemodialysis patients show different levels of serum zinc concentration and supplementation is not necessary for all except for zinc-deficient patients.[134]

Natural Antioxidants

Concentrated red grape juice as a source of polyphenols increased antioxidant capacity, cholesterol standardized α-tocopherol concentration, HDLC, and apolipoprotein A-I and also decreased oxidized LDLC, LDLC, and apolipoprotein B-100 in hemodialysis patients. So it has favorable effects in cardiovascular risk reduction.[135] The effect of regular dietary supplementation with concentrated red grape juice in lowering neutrophil NADPH-oxidase activity and plasma concentrations of oxidized LDLC was greater than vitamin E in these patients.[136] In an experimental kidney failure study, green tea extract, as a safe antioxidant, showed a direct effect on cardiac myocyte and prevented ROS production and development of cardiac hypertrophy.[137] Silymarin in combination with vitamin E reduced malondialdehyde and increased erythrocyte GP and hemoglobin levels in ESRD patients.[138]

Other Potential Antioxidants

Data from an animal study suggested that accumulation of indoxyl sulfate, a uremic toxin, enhanced intravascular oxidative stress. Administration of AST-120, an oral adsorbent, could attenuate oxidative stress by reducing levels of indoxylsulfate in CKD models.[139] Nakamura and coworkers demonstrated that administration of AST-120, 6 g/d, protected tubular injury in nondiabetic CKD patients by reduction in proteinuria and ROS generation.[140] Administration of estrogen could be effective in suppressing CKD-induced systemic inflammation through its antioxidant and anti-inflammatory properties.[141] Exogenous administration of a newly recognized intrinsic antioxidant, 5-hydroxy-1-methylimidazolidine-2,4-dione, in an animal study, prevented the initiation and progression of chronic renal failure by inhibiting CKD-induced oxidative stress.[142]

CONCLUSIONS

Both classical CVD risk factors and uremia-specific risk factors are associated with CKD. Chronic volume expansion, anemia, altered calcium and phosphorous metabolism, hyperhomocysteinemia, inflammation, increased oxidative stress, malnutrition, and uremic toxins are nontraditional CVD risk factors in CKD patients. Oxidative stress is prevalent in CKD patients and is considered to be an important pathogenic mechanism. Oxidative compounds are produced as part of tissue repair processes, inflammation and defense mechanism, but in pathological situations such as uremia, chronic improper activation of oxidative processes contributes to cell and tissue injury.[6] Considering oxidative stress and detecting these phenomena by measuring different biomarkers in clinical setting could help to explain high prevalence of CVD in CKD patients, and also they may present new target for therapeutic intervention and also recommendation of routine use of antioxidants in these at risk population.

CONFLICT OF INTEREST

None declared.

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