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Oxidative stress in chronic kidney disease

Xiao Chun Ling[1] and Ko-Lin Kuo[2,3*]

Abstract

For patients with chronic kidney disease (CKD), the leading cause of mortality is cardiovascular disease. One of the main novel risk factors is oxidative stress, which occurs when there is overproduction of reactive oxygen species (ROS) and/or a reduction in antioxidant defense capacity. Oxidative stress is involved in the progression of renal injury, pathogenesis of atherosclerosis, and exacerbation of disease burden in CKD patients. In addition, uremic- and dialysis-associated factors in these patients further contribute to oxidative stress via a proinflammatory state, including exposure to dialysate endotoxins or the use of bioincompatible hemodialysis dialyzer membranes. Consequences of oxidative stress in CKD patients include atherosclerosis, amyloidosis, and anemia. Strategies to combat oxidative stress include antioxidant therapies such as vitamins C and E or *N*-acetylcysteine (NAC). While these antioxidant strategies are promising, few interventional studies have examined their effects until now. In light of the disparate experimental and clinical data, large, randomized, long-term studies are required to establish their efficacy and safety in CKD patients.

Keywords: Chronic kidney disease, Dialysis, Oxidative stress

Background

Today, more than 2 million people globally have chronic kidney disease (CKD) [1], with most undergoing hemodialysis (HD) or other forms of renal replacement therapy [2]. For CKD patients, the leading cause of mortality is cardiovascular (CV) disease [3]. Well-known risk factors, such as diabetes, hypertension, and dyslipidemia, have been established to be strongly associated with CV disease in CKD patients. However, these traditional risk factors in the Framingham predictive instrument do not accurately predict coronary events in CKD [4]. Moreover, the study of Artherosclerosis Risk in Communities (ARIC) implied that both conventional and novel risk factors are relevant in CKD stage 4 [5]. Studies have shown that novel risk factors are much more prevalent in patients undergoing HD than in the general population [6].

Among the novel risk factors, oxidative stress, which is the overproduction of reactive oxygen species (ROS) and/or a reduction in antioxidant defense capacity, is well documented and studied in uremic patients. It might be implicated in artherosclerosis pathogenesis, cardiovascular events, and other CKD-related complications such as endothelial cell dysfunction, anemia, and protein-energy wasting. In this review article, we present updated evidence to show that increased oxidative stress places a significant burden on patients with CKD. In addition, we review the utilization of certain biomarkers to enable us to better manage oxidative stress in CKD and present novel clinical management methods in order to improve patient outcomes.

Oxidative stress in CKD

Oxidative stress arises when there is an imbalance between free radical production and antioxidant defense. As a result, certain biomolecules are oxidized, leading to structural and functional modifications of these molecules [7]. This oxidant production process occurs mainly in the mitochondria, with the help of mitochondrial cytochrome oxidase enzymes such as cytochrome P450. The ROS products from these processes likely contribute to the progression of renal injury and the pathogenesis of atherosclerotic diseases in CKD [8].

The primary ROS responsible for oxidative stress are superoxides (•O2). The major source of superoxides is the production by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in phagocytes and endothelial cells. Superoxides are removed by superoxide dismutase (SOD) by conversion to hydrogen peroxide (H_2O_2). Studies have shown significant upregulation of NADPH oxidase

* Correspondence: kolinkuo8@gmail.com
[2]Division of Nephrology, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, No.289, Jianguo Rd., Xindain Dist, New Taipei City 23142, Taiwan
[3]School of Medicine, Tzu Chi University, No.701, Sec. 3, Jhongyang Rd., Hualien 97004, Taiwan
Full list of author information is available at the end of the article

and downregulation of SOD in CKD, implying that an increase in superoxides is associated with oxidative stress in renal insufficiency [9]. In addition, superoxide anions will react with nitric oxide (NO) to produce peroxynitrite ($ONOO^-$), which causes nitrosative stress. H_2O_2 and chloride ions (Cl^-) are further metabolized by myeloperoxidase to hypochlorous acid (HOCL), thereby contributing to chlorinated stress. Increased formation of advanced glycosylation end products (AGEs) in renal dysfunction can also lead to increased carbonyl stress, which can further initiate inflammation in CKD.

Other factors that might contribute to elevated ROS production in CKD include reduced NO production, hypertension and angiotensin II activity [10-12]. The significance of ROS in CKD progression has been further shown in studies in which antioxidants, including niacin, melatonin, and omega-3 fatty acids, protected against renal injury [13-15].

Oxidative stress pathways in CKD

Currently, four distinct pathways of oxidative stress have been identified: (i) classical oxidative stress, (ii) chlorinated stress, (iii) nitrosative stress, and (iv) carbonyl stress (Fig. 1). Multiple antioxidant enzymes in human cells act as a defense system against oxidative stress, including SOD, catalase, glutathione peroxidase, and nonenzymatic antioxidants. Nonenzymatic antioxidants are categorized as hydrophilic (vitamin C, uric acid, bilirubin, albumin, and flavonoids) or lipophilic (alpha-tocopherol, ubiquinol, and carotenoids) [16, 17].

In uremic patients, the pro-oxidant state arises from reduced antioxidant system (catalase, glutathione peroxidase, glutathione) activity, decreased intracellular vitamin E and vitamin C levels, and decreased levels of high-density lipoproteins, thiols, and apolipoprotein A-I [18, 19]. Increased activity of pro-oxidants is associated with CKD risk factors such as old age, diabetes, chronic inflammatory state, uremic toxins, and dialysis membranes and solutions [8].

Overall, the aforementioned factors will increase oxidative stress in CKD patients, contributing to cellular damage and predisposing the patient to various comorbidities. For instance, impairment of endothelium-derived NO activity in oxidative stress damage will occur, resulting in an early mechanism in the pathogenesis of atherosclerosis in CKD. Figure 1 summarizes the various pathways of oxidative stress formation and the major mechanisms through which clinical consequences were caused.

Pathogenic factors of oxidative stress damage in CKD

Oxidative stress pathogenesis in CKD patients has been well established by current literature, as indicated by the

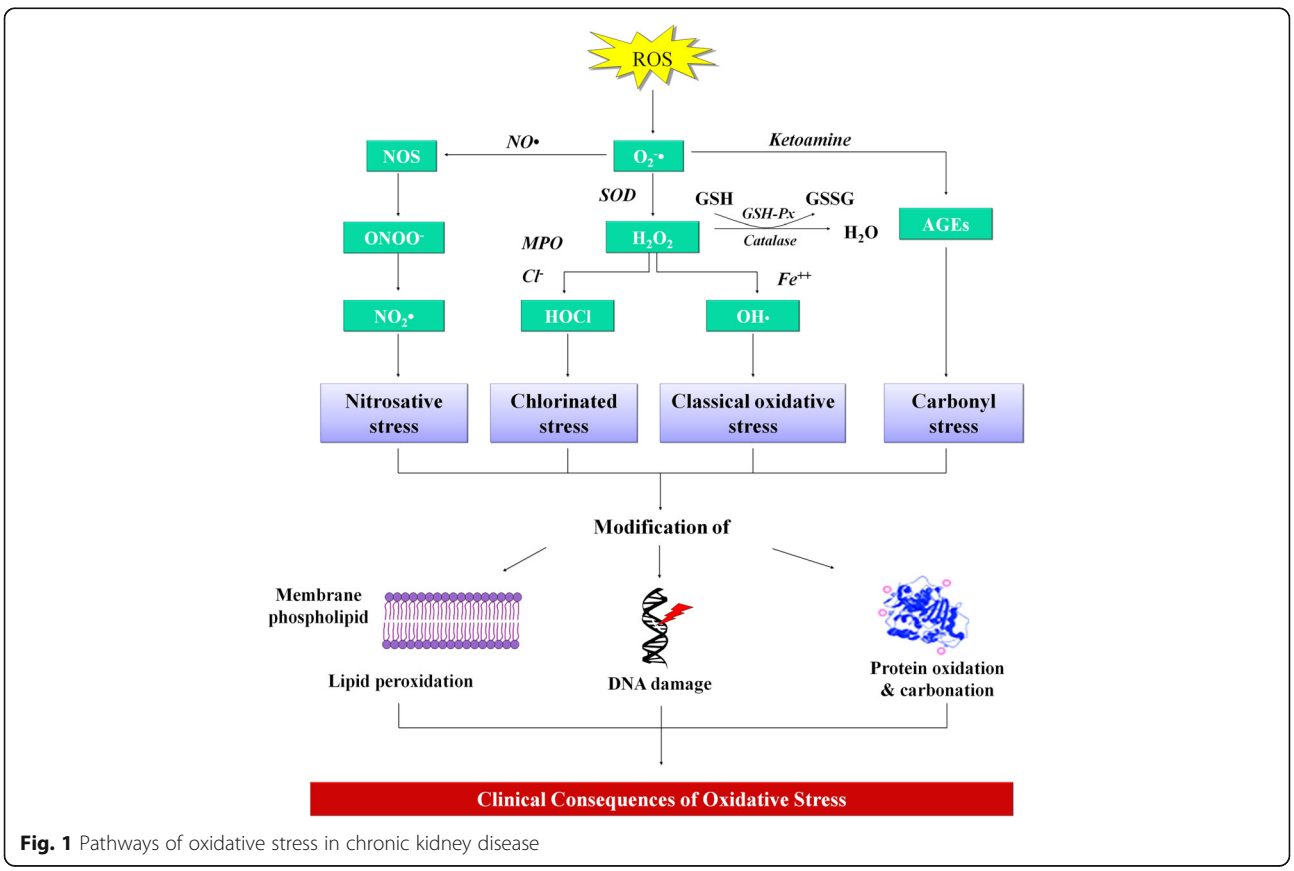

Fig. 1 Pathways of oxidative stress in chronic kidney disease

following: (i) increased concentrations of circulating biomarkers such as lipids, proteins, and nucleic acids in CKD patients; (ii) impaired antioxidant defense due to an inability to remove ROS; and (iii) the occurrence of oxidative stress markers in atherosclerotic CKD patients. The role of oxidative stress in the pathogenesis of cardiovascular diseases in uremic patients is often discussed [8]. A pro-oxidant state can occur as early as in CKD stage 3, as evidenced by reported increases in circulating oxidative stress biomarkers [20]. In correlation, oxidative stress can further contribute to renal function decline via inflammation (activation of NF-κB) [18], hypertension [19], glomerular filtration barrier damage [21], and fibrosis.

Oxidative stress damage is further compounded in patients requiring dialysis therapy due to the bio-incompatibility of dialysis membranes in HD or solutions in PD [22, 23]. The key processes predisposing the production of ROS in CKD patients are summarized in Fig. 2. The complex pathogenesis of oxidative stress in CKD patients can be further categorized into uremia- and dialysis-related factors.

Uremia-related factors

Uremic toxins can be a source of oxidative stress in patients with CKD. Retention of these toxins promotes systemic inflammation via priming polymorphonuclear leukocytes and stimulating CD-8$^+$ cells [24]. Leukocytes of uremic patients were reported by Ward et al. [23] to be primed for superoxide anion production via phorbol myristate acetate (PMA). Resting serum levels of superoxide anions were shown to be higher in patients with chronic HD than in health controls [25]. Oxidative stress is further exacerbated when these molecules accumulate in the context of renal dysfunction and thus provoke further inflammatory responses. Emerging clinical evidence has revealed that oxidative stress and inflammation correlate with adverse outcomes among CKD patients [20, 26, 27].

Additional associative factors of oxidative stress in CKD include low serum selenium concentration, low platelet glutathione peroxidase (GPx) activity [7, 28], and lower serum levels of glutathione [28]. Elevated concentrations of endogenous nitrogen oxide species (NOS) inhibitors due to pronounced disturbance of the nitric oxide (NO) system in CKD contribute to an increased risk of cardiovascular events. Asymmetric dimethyl arginine, which inhibits endothelial NO and promotes ROS production in endothelial cells [29], serves as a major independent risk factor in ESRD [30].

Dialysis-related factors

A pivotal factor of ROS production is the bio-incompatibility of HD systems. In general, two major components of an HD system can contribute to oxidative stress: the dialyzer membrane and trace endotoxins in the dialysate [28, 31, 32]. Alternatively, in the PD system, the glucose-based solutions have a low pH and a high osmolality, which have a negative impact on the biological functions of peripheral phagocytes. Oxygen metabolism of peripheral phagocytes is activated and increased when the cells contact the peritoneum via bioincompatible dialysates [22]. This leads to overproduction of ROS such as $\bullet H_2O_2$ and superoxide anions.

In addition, in certain HD modalities that use highly permeable membranes, there is a loss of solutes, trace elements, and antioxidants. These losses are relevant for hydrophilic and unbound small molecules, including vitamins, thus leading to the observed impairment of enzymatic antioxidants in uremic patients. HJ Lee et al. reported the introduction of several potentially toxic hydrocarbons and halocarbons, such as CH_2Cl_2 or $CHCl_3$, into patients from the dialyzer and tubing sets [33]. Poor quality dialysis solvent and back-diffusion of contaminants also predispose a patient to possible endotoxin exposure. This issue was further evidenced

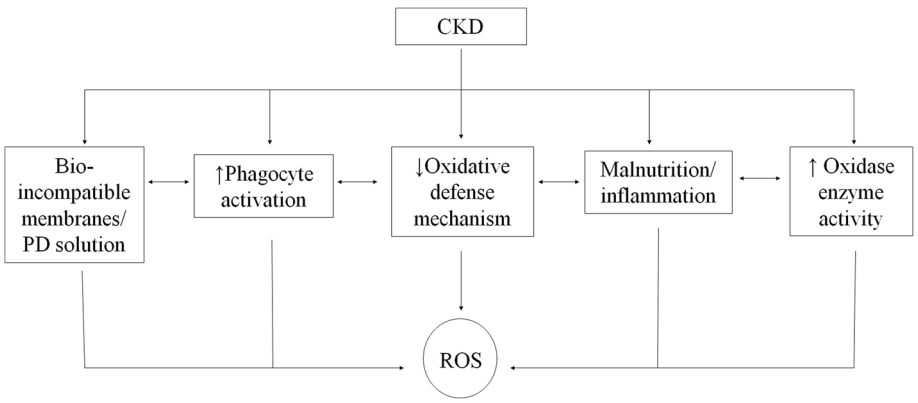

Fig. 2 Pathogenic factors leading to oxidative stress. The oxidase enzymes include cytochrome P450, NADPH oxidase, and xanthine oxidase, and the oxidative defense mechanisms include vitamins C and E, glutathione, SOD, and catalase

by improvements in nutritional status, decreases in the levels of inflammatory markers, and slower decreases in residual kidney function when an ultrapure dialysis system was used instead [34, 35].

Biomarkers of oxidative stress in CKD patients

Damage caused by oxidative stress includes structural and functional modifications to cellular constituents, such as membranous lipids, proteins, and DNA. Thus, it is imperative to clinically measure and predict the risk of complications in CKD patients due to oxidative stress. However, due to the low concentration, highly reactive nature and short half-life of ROS, direct measurements in vivo are difficult. Thus, the oxidative by-products of ROS reaction pathways and of antioxidant concentrations are measured instead.

Commonly used circulating biomarkers include oxidized low-density lipoprotein (ox-LDL), AGE, and oxidized thiol compounds. These ROS pathway by-products can potentially contribute to CV pathogenesis, inflammation, and other uremic complications in CKD patients [36, 37]. In advanced CKD, lipoproteins are more likely to undergo further oxidation to become ox-LDL, which is a potent proinflammatory agent and is highly correlated with artherosclerosis pathogenesis [38, 39]. In addition, Morita Y et al. reported that a high plasma LDL level is a major risk factor for a reduced GFR in normal subjects, suggesting complex interplay among CKD, oxidative stress, and CVD [36]. Another indicator of oxidative stress is low plasmalogen levels, which have been reported in malnourished CKD patients [40].

Malondialdehyde (MDA) was reported to be elevated in HD patients compared to healthy subjects [41, 42]. Matsuda et al. revealed that CKD patients had poorer clinical cardiovascular outcomes in association with enhanced inflammation and oxidative stress, as evidenced by their elevated MDA-modified LDL levels and peak serum C-reactive protein (CRP) [43]. Increased plasma levels of asymmetric dimethylarginine (ADMA), a methylated product of arginine, have been associated with increased CVD in CKD patients [44].

Biomarkers related to DNA damage by ROS in CKD patients include 8-hydroxydeoxyguanosine (8-OH-dG) and 8-oxodeoxyguanosine (8-oxo-dG). These two biomarkers are paramount to measure endogenous oxidative damage to DNA. They also serve as agents in the initiation and promotion of carcinogenesis [45]. 8-OH-dG is clinically measurable in human samples such as in urine samples or even the bloodstream [46, 47].

Advanced oxidation protein products (AOPPs) were identified in the plasma of uremic patients by Witko-Sarat et al. [37] AOPPs are products primarily derived from serum albumin in the event of free radical attack and provide evidence that oxidative stress can result from direct damage to proteins. Declining renal function was associated with increase in AOPP levels, thus making them good markers of CKD progression [37, 48]. Table 1 delineates the most commonly used circulating biomarkers of oxidative stress.

The aforementioned biomarkers had shed light on how degrees of oxidative stress correlate to progression of CKD as well. In the early stages of CKD, different markers such as AOPPs, MDA, and plasma F2-isoprotanes can already be detected. These biomarkers are found in increasing levels in patients with declining degrees of renal function, up till end-stage diseases [49, 50]. This supports the notion that oxidative stress increases as stages of CKD progress. In addition, Tarng et al. reported increasing levels of 8-OH-dG in leukocyte DNA from healthy controls to undialyzed CKD patients, with the highest levels found in HD patients [51]. Besides, erythropoietin (EPO) and 1,25-$(OH)_2D_3$—hormones produced predominantly by the kidney—are found in progressively reduced concentrations as CKD worsens [52].

As mentioned previously, a chronic inflammatory state is induced in CKD. To ascertain the presence of inflammation, one or more involved components, such as C-reactive protein (CRP), interleukin-6 (IL-6), or interleukin-1 (IL-1), can be measured [53]. These markers of inflammation provide higher specificity than biomarkers such as serum albumin or white blood cell count but are more expensive and not readily available in clinical practice.

In the past decade, clinical proteomics technologies, such as protein arrays and SELDI [54], are expected to provide new diagnostic markers that can translate into improved clinical testing. However, the suitability and availability of these technologies require more constructive investigation and discussion before application in the clinical setting.

Clinical consequences of oxidative stress in CKD

The major clinical consequence of oxidative stress in CKD patients is the promotion of long-term complications such as artherosclerosis, amyloidosis, and anemia. As mentioned above, there are multiple mechanisms by which oxidative stress can contribute to the pathogenesis of multiple comorbidities. Most of these mechanisms are mediated through a chronic inflammatory state induced by CKD. As a result, there is a purported strong association between the levels of inflammatory markers in CKD patients and adverse outcomes as outlined below.

Artherosclerosis

Cardiovascular disease is the leading cause of mortality in CKD patients.

Both cellular and subcellular mechanisms by which inflammation induces artherosclerosis have been established based on the current literature [55]. The uremic

Table 1 Circulating biomarkers of oxidative stress

Types	Biomarkers of oxidative stress	
Lipids	• Malondialdehyde (MDA) • Oxidized low-density lipoprotein (ox-LDL) • Lipid hydroperoxides	• Advanced lipoxidation end products (ALEs) • Cholesteryl ethers • 4-hydroxynonenal (HNE)
Arachidonic acid derivatives	• F_2-isoprostane • Isolevuglandins	• Isofurans
Carbohydrates	• Reactive aldehydes	• Advanced glycosylation end products (AGEs)
Amino acids	• Cysteine • Homocysteine • Nitrotyrosine	• Chlorotyrosine • Isoaspartate • Carboxymethyl lysine
Proteins	• Advanced oxidation protein products (AOPPs) • Protein thiols oxidation	• Carbonyl formation • Amine oxidation
Nucleic acids	• 8-hydroxy-2′-deoxyguanosine (8-OH-dG)	• 8-Oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG)

state predisposes CKD patients to accelerated atherosclerosis and reduced NO bioavailability in vascular tissues. Steinberg et al. showed that the atherogenicity of LDL can be modified via oxidative stress [56]. Through scavenger receptors, oxidized LDL molecules were taken up, and the transformation of monocytes to foamy cells was potentiated. The proliferation of vascular smooth cells and the production of inflammatory cytokines subsequently followed. In addition, reduced NO availability resulted from the reaction of superoxide anion with NO in patients with higher oxidative stress [57]. This event causes endothelial cell dysfunction and, ultimately, atherosclerosis.

In CKD patients, uremic retention solutes such as guanidine, *p*-cresol, indoxyl sulfate, and asymmetric dimethylarginine (ADMA) have been suggested to have proatherogenic properties [58]. They contribute to cardiovascular events via inhibiting endothelial NO production and promoting superoxide production. Maggi et al. showed that LDL isolated from CKD patients is more susceptible to in vitro peroxidation than LDL from healthy subjects [59]. In lipid peroxidation, acrolein, thiobarbituric acid reactive substance (TBARS), 4-hydroxynonenal, and malondialdehyde are produced [60]. There was a significant elevation in malondialdehyde levels in CKD patients with cardiovascular disease compared to CKD patients without cardiovascular disease, further suggesting that oxidative stress potentiates artherosclerosis in CKD [61].

Anemia

Anemia is regarded as a nearly universal complication of CKD. While the rate of red blood cell production is reduced in CKD, shortened red blood cell life span also contributes to renal anemia. Increased peroxidation in CKD due to oxidative stress can lead to a profound modification of cellular structures and function, impairing erythrocytes. Serum levels of MDA in erythrocytes are higher in HD patients, as shown in previous studies, along with severe vitamin deficiency, thus explaining the shortened lifespan of erythrocytes in CKD patients [62].

In a study with 107 consecutive HD patients, serum levels of MDA, protein carbonyls, and 4-hydroxynonenal were inversely proportional to hemoglobin levels. The correction of renal anemia by epoetin subsequently reduced the serum levels of aldehydic lipid peroxidation products [63]. Another study revealed that antioxidant therapy improved the renal anemia in CKD patients while reducing their requirement for erythropoiesis-stimulating agents (ESAs) [64, 65].

In recent years, intravenous (IV) iron supplementation has been increasingly recognized as a therapy for anemia in CKD patients. The key component of this treatment is to enhance the efficacy of erythropoiesis-stimulating agents (ESAs) by reducing the requirement for ESAs, increasing hemoglobin levels and improving the cost-effectiveness of ESA treatment [65]. However, since iron is a cellular transition element and its ionic forms participate in electron transfer reactions, it can also produce free radicals. Our prospective cohort study showed that iron supplementation was associated with a lower risk of all-cause mortality in CKD patients [66]. The survival benefit of iron use was consistent across the majority of dosage groups, except for those who were treated with monthly IV iron > 200 mg. The general benefits of iron treatment revealed in other studies included achieving target hemoglobin levels, reducing hospitalization and improving survival [67–69]. The clinical decision to use IV iron therapy should be based on a risk-benefit analysis [52].

Amyloidosis

Under conditions of oxidative stress, ROS tend to modify the function of proteins directly via the formation of oxidized amino acids. ROS can also react with other substrates to form potent pro-oxidant species, such as AGEs. AGEs promote the alteration of vascular structure and function while further enhancing oxidative stress and inflammation. Besides, the presence of AGEs in β2-microglobulin deposits in long-term HD patients

suggests that protein denaturation from oxidative stress might increase the risk for amyloidosis [68].

Protein-energy wasting syndrome

Nutritional status decline is highly prevalent in CKD and is usually associated with high rates of morbidity and mortality. For CKD patients, the International Society of Renal Nutrition and Metabolism (ISRNM) had proposed a common nomenclature and diagnostic criteria for protein-energy wasting syndrome (PEW), a condition of concurrent losses of protein and energy stores with cachexia as the end stage [70]. While there are many contributing factors of PEW in CKD, such as decreased intake, anabolism, and other comorbidities, increased oxidative stress in CKD is being considered one of the major causes.

Increased oxidative signaling is associated with muscle insulin resistance, atherosclerosis, and muscle wasting [71, 72]. Upregulation of NADPH oxidases in CKD creates signals to induce muscle insulin resistance [73]. Elevated inflammatory markers in CKD is also associated with loss of muscle mass [73]. Besides, there is increased oxidation of protein, lipid, and DNA due to depletion of dietary antioxidants, protein stores, and systemic inflammation in CKD [71, 72].

Immunodeficiency

As oxidative stress in CKD leads to a chronic inflammatory state, the coordination between polymorphonuclear leukocytes (PMNLs), lymphocytes, and antigen-presenting cells (APCs) can be impaired, leading to decline in host defense responses. Uremia disrupts the priming of immune cells and enhances apoptosis of PMNLs [74, 75]. Besides, as demonstrated in vitro, monocytes from HD patients have characteristics of senescent cells, suggesting an increased susceptibility to apoptosis [76]. Terminal differentiation of monocyte-derived dendritic cells in CKD stage IV patients is also affected [77]. Lim et al. has shown that dendritic cells, when exposed in uremic microenvironments, exhibited decreased endocytosis and impaired maturation [78].

Medications against oxidative stress in CKD patients

To combat oxidative stress and its clinical consequences in CKD patients, the use of antioxidants is vigorously promoted. The two primary goals of antioxidative stress management are to slow the progression of CKD and to reduce its clinical consequences, such as atherosclerosis. Table 2 summarizes the relevant clinical studies on antioxidant therapies discussed here.

N-acetylcysteine (NAC)

Ivanovski et al. demonstrated that treatment with *N*-acetylcysteine (NAC), which is a precursor to the antioxidant glutathione, can reduce nitrosative oxidative stress and atheromatous plaque progression in a murine model of CKD-accelerated atherosclerosis [79]. NAC pretreatment was shown to reduce endothelial dysfunction due to uremic toxins by decreasing ROS-induced expression of NF-κB [80]. In a mouse model of diabetic nephropathy, NAC reduced renal MDA levels [81]. Possible beneficial

Table 2 Summary of clinical studies on antioxidant therapies

Study [year]	Intervention (dosage)	Subjects (study length)	Effect
N-Acetylcysteine (NAC)			
Tepel et al. [83] [2003]	Acetylcysteine (600 mg twice per day)	134 HD patients (2 years)	a) Ischemic stroke reduced by 36% b) Cardiac events reduced by 30%
Nolin et al. [84] [2010]	Sustained-release NAC (600 mg or 1200 mg twice per day for 14 days)	24 ESRD patients	Significant reduction in total homocysteine plasma concentrations
Vitamins C and E			
Boaz et al. [88] (SPACE study) [2000]	High-dose α-tocopherol (800 IU daily)	196 HD patients with pre-existing cardiovascular disease (median 519 days)	a) Significant reduction in myocardial infarctions and other cardiovascular events b) No significant difference in overall survival
Tarng et al. [91] [2004]	Vitamin C (300 mg thrice weekly for 8 weeks)	60 HD patients	Significant decrease in mean 8-OH-dG levels
Morimoto et al. [85] [2005]	Vitamin E-coated polysulfone membrane (18 months)	31 HD patients	Significant reduction in ADMA, ox-LDL and MDA-LDL levels compared to baseline
Nanayakkara et al. [89] (ATIC study) [2007]	Regimen of pravastatin, vitamin E and homocysteine-lowering therapy	93 patients with eGFR $< 38 \pm 15$ mL/min/1.73 m^2 (2 years)	a) Significant reduction in common carotid intima-thickness and albuminuria b) No effect observed in renal function
Takouli et al. [90] [2010]	Vitamin E-coated cellulose acetate membrane (3 months)	9 HD patients	a) Significant decrease in Hs-CRP, d-ROMs and IL-6 levels b) Significant increase in total antioxidant capacity and SOD levels

Abbreviations: *HD* hemodialysis, *ESRD* end-stage renal disease, *8-OG-dG* 8-hydroxy-2'-deoxyguanosine, *ADMA* asymmetric dimethylarginine, *ox-LDL* oxidized low-density lipoprotein, *MDA-LDL* malondialdehyde-modified low-density lipoprotein, *Hs-CRP* high-sensitivity C-reactive protein, *d-ROMs* reactive oxygen metabolites and derivatives, *SOD* superoxide dismutase, *ESA* erythropoiesis-stimulating agent

effects of NAC were shown by an increase in hematocrit and decreases in 8-isoprostane and ox-LDL in HD patients on NAC therapy [82]. Besides, Tepel et al. reported that composite cardiovascular end points, such as cardiac events and ischemic stroke were reduced by 30 and 36%, respectively, with oral NAC treatment [83]. However, the role of NAC in long-term therapy to reduce oxidative stress complications in CKD patients might be limited due to reduced clearance of NAC in these patients [84].

Vitamins E and C

Two of the most commonly known antioxidants are vitamins C and E. Vitamin E can protect cell membranes from lipid peroxidation, and vitamin C can directly scavenge ROS (superoxide anions and hydroxyl radical). A number of small clinical studies have reported that the administration of vitamins E and C can help reduce levels of oxidative stress biomarkers. Morimoto et al. reported that polysulfone membranes coated with vitamin E exerted antioxidant activity via reducing ADMA in HD patients [85]. The goal of vitamin E supplementation is to increase α-tocopherol levels in plasma membranes, as it is a compound with the highest bioavailability in the class of vitamin E. In CKD patients, serum α-tocopherol levels are markedly decreased, suggesting an increased need for α-tocopherol in this population [86]. In terms of clinical benefits, α-tocopherol supplementation has been shown to reduce the risk of cardiovascular diseases and to increase erythrocyte antioxidants [87]. The Secondary Prevention with Antioxidants of Cardiovascular Disease in End-Stage Renal Disease (SPACE) study by Boaz et al. [88] revealed clinically significant reduction in the myocardial infarctions and other cardiovascular events for HD patients treated with α-tocopherol. In the Anti-Oxidant Therapy in Chronic Renal Insufficiency (ATIC Study) [89], a treatment strategy comprising pravastatin, vitamin E and decreasing homocysteine in order to combat oxidative stress resulted in a significant decline in common carotid intima-media thickness and an improvement in brachial artery flow-mediated dilatation and urinary albumin excretion. These outcomes implied that an active treatment strategy could be useful in safely reducing the burden of cardiovascular events in CKD via targeting oxidative stress.

In addition, Takouli et al. reported that vitamin E-coated acetate dialysis membranes have reduced biomarker levels of oxidative stress and inflammation [90]. A vitamin E-coated dialysis membrane comprises a multilayer membrane with lipid-soluble α-tocopherol on the blood surface side, which allows direct free radical scavenging. In addition, Tarng et al. demonstrated that the use of a vitamin E-bound dialysis membrane can reduce lymphocyte 8-OH-dG levels and preserve plasma vitamin E concentration, suggesting a reduction in oxidative stress [91].

Conclusion

Existing preclinical and clinical studies have established that oxidative stress plays an important role in CKD. In addition to being an important pathogenic mechanism, oxidative damage is further complicated by uremic status, the dialysis system, and concomitant comorbidities related to CKD patients. Anemia, malnutrition, and other systemic inflammatory processes are associated with oxidative stress. Several clinical biomarkers have been helpful in investigating the degree of oxidative stress in CKD, but their clinical application remains to be further investigated. Various therapeutic strategies have emerged, such as the antioxidants vitamins E and C. Current clinical evidence seems promising, but large-scale, randomized controlled trials with long-term follow-up periods will be required to reach a definitive decision on management options.

Abbreviations

AGEsa: Advanced glycosylation end products; GSH: Reduced glutathione; GSH-PHX: Glutathione peroxidase; GSSG: Oxidized glutathione; MPO: Myeloperoxidase; NADPH: Nicotinamide adenine dinucleotide phosphate; NOS: Nitric oxide synthase; SOD: Superoxide dismutase

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Availability of data and materials

Not applicable

Authors' contributions

The contributions of each author: K-LK has devised, designed, and overseen the process of the review; XCL has written the drafts of the manuscript. All authors have contributed to subsequent versions and approved the final article; K-LK is the study guarantor. Both authors have read and approved the manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Author details

[1]School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan. [2]Division of Nephrology, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, No.289, Jianguo Rd., Xindain Dist, New Taipei City 23142, Taiwan. [3]School of Medicine, Tzu Chi University, No.701, Sec. 3, Jhongyang Rd., Hualien 97004, Taiwan.

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