ACCSCIENCE PUBLISHING

Eurasian Journal of Medicine and Oncology

REVIEW ARTICLE

Oxidative stress and renal biology: Unraveling the bidirectional link with aging and chronic kidney disease

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Citation: Akhoundiasl S, Afandideh F, Mahmoodpoor F, *et al*. Oxidative stress and renal biology: Unraveling the bidirectional link with aging and chronic kidney disease. *Eurasian J Med Oncol.* 2026;10(3):025450475. doi: 10.36922/EJMO025450475

Received: November 8, 2025

Revised: December 4, 2025

Accepted: December 10, 2025

Published online: April 8, 2026

Abstract

Excessive levels of reactive oxygen and nitrogen species cause cellular injury, termed oxidative stress. This occurs due to an imbalance between the prooxidant and antioxidant capabilities of the cell. Mounting evidence suggests a strong connection between aging, oxidative stress, and age-mediated diseases, including chronic kidney disease (CKD). The global prevalence of CKD has shown an increasing trend, especially among the elderly. Under physiological conditions, homeostatic mechanisms limit oxidative stress and repair oxidant-induced damage. However, in CKD, oxidative stress is not mitigated but worsened due to the disruption of homeostasis, particularly with aging. CKD also accelerates aging through several mechanisms, including oxidative stress. In turn, oxidative stress can contribute to CKD as the principal cellular factor. Besides, CKD and its comorbid conditions can result in inflammation, oxidative stress, apoptosis, and necrosis, which stimulate premature senescence in multiple body organs. Unraveling the potential mechanisms of CKD and the role of oxidative stress in CKD pathology in aging patients necessitates an inclusive discussion of current research. In this review, we summarize previous studies and discuss the role of oxidative stress and its implications in the pathogenesis of CKD during both premature and normal aging.

Keywords: Chronic kidney disease; Aging; Inflammation; Vascular diseases; Oxidative stress; Reactive oxygen species

1. Introduction

The kidneys show more age-related degradation than most other organs, even in the absence of heart disease.[1] This degradation is commonly observed as a decline in the function, increased fibrosis, and loss of one-fourth of the renal mass, especially from the renal cortex.[1,2] Although the exact molecular mechanisms causing this age-related loss of functional cells are unknown, they seem to be related to modifications in proliferative and apoptotic pathways. Age-related atrophy is associated with decreased cellular proliferation and increased apoptosis. These effects can be caused by shortened telomeres, downregulation of genes responsible for generating antioxidants, reduced mitogen reactivity, and changed expression of proteins involved in cell adhesion and cytoskeletal dynamics. Furthermore, senescence is associated with decreased sensitivity to harmful stimuli and mitogens, contributing to apoptosis and reduced proliferation.

In essence, aging and chronic kidney disease (CKD) mutually influence each other: aging leads to CKD, CKD contributes to premature aging, and their interplay is connected through oxidative stress. Although oxidative stress, aging, and CKD are often discussed together, this review focuses on two closely related themes. First, rather than discussing oxidative stress in general terms, we examine its precise role in driving the so-called oxi-inflammaging axis in CKD. We examine how mitochondrial dysfunction and disrupted organelle communication—like issues at mitochondria-associated membranes—help perpetuate this cycle, pushing the kidney towards a prematurely senescent state. Second, we aim to fill a gap in current understanding: why broad antioxidant therapies repeatedly fail in trials, while newer cardiorenal-protective drugs, such as sodium–glucose cotransporter 2 (SGLT2) inhibitors and finerenone, show clear benefits. We discuss the idea that these drugs do not simply remove reactive oxygen species (ROS); instead, they act on the sources, targeting the roots of oxidative stress. By combining recent clinical trial results with evolving molecular insights, this review offers a fresh perspective on CKD as a model of accelerated aging and highlights therapeutic strategies that combat this harmful cascade.

2. Literature search strategy

The purpose of this narrative review is to identify the bidirectional relationships among oxidative stress, aging, and CKD. We conducted a comprehensive search of the literature to identify eligible studies for generating an overview of the current evidence. To this aim, we searched PubMed/MEDLINE, Scopus, and Web of Science for papers published between January 2000 and December 2025. The following Boolean search string was used: ("oxidative stress" OR "reactive oxygen species" OR "ROS" OR "antioxidant") AND ("aging" OR "senescence" OR "inflammation") AND ("CKD" OR "chronic kidney disease" OR "chronic renal disease" OR "renal fibrosis" OR "uremia"). The "AND" and "OR" Boolean operators were used to narrow the search. Original research, experimental or clinical reports, reviews, and meta-analysis articles published in English were included. Articles in a language other than English, studies on different topics, and those without full-text availability were excluded. The titles and abstracts of the studies were searched for relevance, followed by a full-text review. We summarized major findings, mechanisms, and concepts related to oxidative stress, aging, and CKD. We also manually searched the reference lists of the included studies to identify additional studies that may have been overlooked.

3. Oxidative stress

The interaction of oxygen with specific molecules can generate free radicals by donating or accepting single electrons.[3] ROS, which can initiate the generation of reactive nitrogen species (RNS), as well as well-defined free radicals produced in aerobic cells, are intertwined with aging and age-related human diseases.[4] ROS and RNS are also involved in normal physiological processes, including the extraction of adenosine triphosphate (ATP) from organic molecules, the stimulation of the immune system, and various signaling pathways.[5] There are both endogenous and exogenous sources of ROS. Myeloperoxidase, lipoxygenase, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase are cytoplasmic sources of endogenous ROS.[6] Superoxide is generated during mitochondrial respiration and by specific enzymes, particularly NADPH oxidases (NOX family), which use NADPH as an electron donor. Hydrogen peroxide (H_2O_2) can induce the formation of extremely reactive hydroxyl radicals via metal-ion catalysis, predominantly through the Fenton reaction (ferrous ion or other transition metals required) and the Haber–Weiss cycle. These radicals can particularly react with vital cellular macromolecules, such as proteins and membrane phospholipids. Hypochlorous acid can also be formed from H_2O_2 in the presence of myeloperoxidase and chloride, which can specifically disrupt the structure of proteins.[5] Finally, superoxide and nitric oxide (NO) react to form peroxynitrite ($ONOO^-$), a potent oxidant as well, resulting in an augmentation of RNS levels. This directly scavenges NO and decreases its vasodilating potential, as well as promoting nitrosative stress. $ONOO^-$ can oxidize its cofactor, tetrahydrobiopterin, required for endothelial NO synthase (eNOS), resulting in eNOS uncoupling and

paradoxically increasing superoxide and decreasing NO production. It also hinders essential proteins responsible for vasorelaxation and mitonchoindrial function via tyrosine nitration, causing significant damage during endothelium-dependent hyperpolarization.[6] On the other hand, there are numerous xenobiotics that are considered exogenous sources of ROS.[7]

Reactive oxygen species, whether endogenous or exogenous, can induce oxidative damage to cellular elements, and their serum or tissue levels can serve as markers of oxidative stress.[8] Proteins can undergo various oxidative modifications. Oxidation of proteins through specific amino acids (lysine, arginine, proline, and threonine) produces protein carbonyls.[9] The oxidation of low-density lipoproteins (LDLs) is another pathway to generate free radicals.[10] In addition, polyunsaturated fatty acids can be oxidized to produce different reactive aldehydes, including malondialdehyde, trans-4-hydroxy-2-nonenal, and isoprostanes.[8] Advanced glycation end-products (AGEs) may be formed following a glycoxidation process between amino acids (lysine and arginine) and the carbonyl portions of carbohydrates.[11] Biological systems are protected against reactive species via the antioxidant defense, which can be endogenous or exogenous.[12] Primary endogenous antioxidants include catalase, superoxide dismutase, and glutathione (GSH) peroxidase.[13]

The endogenous antioxidative defense system can be both enzymatic and non-enzymatic. Hydroxyl radical production can be prevented by superoxide dismutase, with the resulting product, H_2O_2, decomposed to water and oxygen via catalase. Furthermore, GSH peroxidase detoxifies peroxide and hydroxyl radical species. GSH, the cofactor for peroxidase, is oxidized to GSH disulfide, which is in turn reduced by GSH reductase. Additional antioxidant enzymes include glucose-6-phosphate dehydrogenase and GSH-S-transferase.[14] Non-enzymatic antioxidants are molecules that can quench free-radical chain reactions by reacting with ROS. In plasma, the main contributors to antioxidant capacity are uric acid and albumin. Other blood-borne antioxidants include β-carotene, α-tocopherol, and bilirubin.[15]

Exogenous antioxidants consist of vitamin C, vitamin E, oil lectins, zinc, and selenium, as well as phenolic acids, flavonoids, resveratrol, and drugs like acetylcysteine. Phenolic antioxidants are stilbene derivatives. Vitamin C scavenges hydroxyl and superoxide radical anions, while vitamin E acts against lipid peroxidation of cell membranes.[16] Overproduction of ROS and/or a fall in antioxidant activity diminishes the cell's capacity to repair induced damage, thereby leading to oxidative stress. However, the failure of systemic antioxidant supplements repeatedly in large-scale clinical trials, despite robust preclinical evidence, points to a critical conceptual gap. The oversimplified model of scavenging ROS completely misses the complex physiological role these molecules play as important signaling mediators—that is, redox biology. Global suppression of ROS disrupts basic cellular processes, including autophagy and immune defense. Most antioxidants also fail to reach the relevant subcellular compartments, for example, the mitochondrial matrix, at effective concentrations. In contrast, the success of finerenone and SGLT2 inhibitors may be related to their ability to modulate the source of pathological ROS, for example, by either inhibiting NADPH oxidase or improving mitochondrial health, rather than indiscriminately neutralizing all ROS. This distinction between source-directed therapy and scavenger-based therapy may be a fundamental reason for their divergent clinical outcomes.[17]

4. Chronic kidney disease: The central role of oxidative stress

Oxidative stress induces ischemia and glomerular destruction in the kidneys, leading to renal damage and the progression of CKD. CKD can also induce endothelial dysfunction and hypertension indirectly via inflammation.[18] CKD is a chronic inflammatory process in which activation of leucocytes (including monocytes and polymorphonuclear neutrophils) upregulates myeloperoxidase and NADPH oxidase, resulting in ROS formation.[19] Superoxide anions released by leukocytes in CKD patients can contribute to hypertension by inactivating NO. Additionally, NO reduction occurs due to a deficit in the L-arginine precursor, which is produced in the kidney from L-citrulline. Superoxide anions can react with NO to form $ONOO^-$. This process oxidizes NO, making it unstable and leading to further production of superoxide.[20]

In CKD, NO synthase (NOS) inhibitors, such as asymmetric dimethylarginine, accumulate and cause inhibition of the NOS activity, leading to vasoconstriction and hypertension.[21] Elevated homocysteine levels in CKD patients contribute to oxidative stress by inducing endoplasmic reticulum stress and activating NADPH oxidase in vascular endothelial cells, as well as promoting asymmetric dimethylarginine production, thereby reducing NO synthesis and increasing the risk of cardiovascular events.[21] This oxidative stress further drives endothelial dysfunction, alters vascular permeability, and promotes the accumulation of oxidized LDL in the intima, contributing to atherosclerosis.[22] Asymmetric dimethylarginine causes endothelial dysfunction leading to proteinuria. The glomerular and kidney damage intensifies

ROS production due to the release of inflammatory cytokines.[19] Additionally, oxidative stress leads to lipid oxidation in red blood cell membranes and a decrease in membrane elasticity, which can increase the likelihood of hemolysis. This process may clarify CKD-induced anemia regardless of diminished erythropoietin synthesis in the kidney.[23] The global prevalence of CKD, predominantly amongst the elderly community, is increasing, thereby accelerating aging in these patients through several mechanisms, particularly oxidative stress.

Cell survival and health require the absence of toxins, preservation of cellular-extracellular matrix interactions, and the absence of the inflammatory response. A reduction in cellular energy can result from an acute or long-term absence of prerequisites for cell survival, leading to apoptosis and necrosis. Other than ATP production, mitochondria generate substantial amounts of ROS and are highly susceptible to damage caused by oxidants.[24] Increased oxidant concentrations in the extracellular niche negatively influence other cells.[24] The kidney appears to play a central role in these reactions, as its health directly influences oxidative balance. Similarly, the mechanisms underlying other chronic renal diseases resemble those observed in aging kidneys. Several factors that can cause both acute and chronic kidney failure are connected with oxidative stress as a partial or full mediating mechanism (Figure 1).[25]

This is a schematic overview of the basic pathways of ROS generation and their consequences in aging and CKD. Included are the following: (i) The significant endogenous, e.g., mitochondrial electron transport chain, NADPH oxidase, and exogenous sources of ROS production; (ii) The oxidative damage to critical cellular macromolecules, including lipids (e.g., forming malondialdehyde), proteins (e.g., for instance, protein carbonyls), and DNA; and (iii) The ensuing activation of harmful cellular processes,

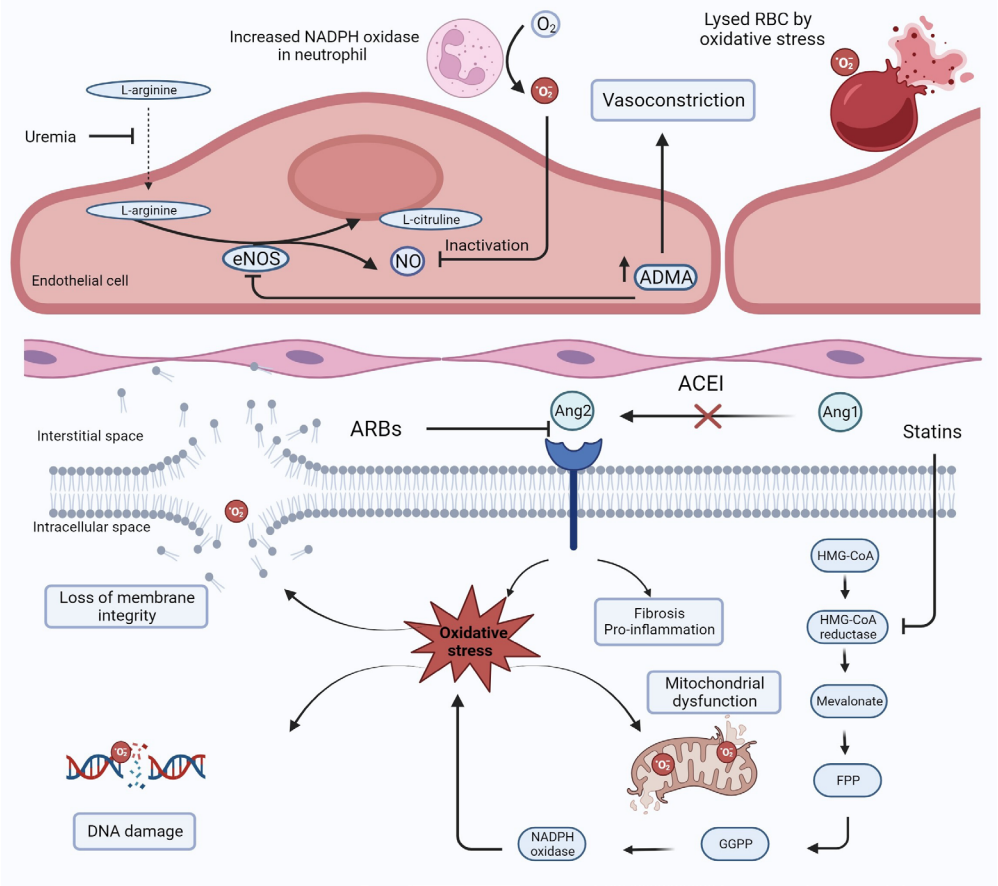

Figure 1. The role of oxidative stress in CKD.
Abbreviations: ACEI: Angiotensin converting enzyme inhibitors; ADMA: Asymmetric dimethylarginine; Ang1/Ang2: Angiotensin I/II; ARBs: Angiotensin receptor blockers; CKD: Chronic kidney disease; eNOS: Endothelial nitric oxide synthase; FPP: Farnesyl pyrophosphate; GGPP: Geranylgeranyl pyrophosphate; HMG-CoA: Hydroxymethylglutaryl-CoA; NADPH: Nicotinamide adenine dinucleotide phosphate; NO: Nitric oxide; RBC: Red blood cell. Figure created by authors using Microsoft powerpoint 2016.

including inflammation, apoptosis, and fibrosis that drive renal aging and CKD progression.

Several common immunosuppressive agents, chemotherapeutic drugs, environmental toxins (e.g., heavy metals), as well as cardiovascular issues such as diabetes, hypertension, hemodynamic dysfunction, generalized vascular stiffening, and intravenous iron-related renal injury, are stress-inducing factors. However, the long-term ramifications of these findings require further research. For instance, intravenous iron is frequently used to treat CKD; however, it also induces oxidative stress, which is associated with short-term proteinuria and tubular damage.[26] The rapid ROS formation implies that free-iron-independent mechanisms are causing both acute renal injury and oxidative stress. The improvement in kidney dysfunction and syndromes with antioxidants suggests the pivotal role of oxidative stress in these conditions. For instance, glomerular, vascular, and tubulointerstitial diseases develop in Zucker diabetic obese rats, which show progressive nephropathy associated with the initiation of oxidative damage. These rats have benefited from the $ONOO^-$ scavenger, ebselen.[27]

Divergent views exist on the advantages of specific antioxidant treatments,[28] and further investigation into the mechanisms and results is necessary before a conclusion regarding the benefits or drawbacks can be made. For instance, Efrati *et al.* (2003) reported that N-acetylcysteine was effective in treating radiographic contrast-induced nephropathy,[29] whereas Boccalandro *et al.* (2003) did not report similar benefit.[30] Numerous investigations have examined the impact of antioxidant supplements on aging and renal diseases. While different *in vivo* studies have demonstrated the effectiveness of vitamin E treatment, the outcomes of human trials have been underwhelming. Several researchers experimenting with commonly prescribed pharmaceuticals are showing encouraging results. These compounds exhibit antioxidant activity that mediates their renoprotective benefits. These substances include the angiotensin II type 1 receptor antagonists candesartan and losartan, as well as the angiotensin-converting enzyme inhibitors quinapril and enalapril.[31,32]

Several statins have also been shown to exert favorable effects on renal diseases. These medications are mostly recognized for their ability to lower cholesterol as they are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Recently, it has been shown that statins may reduce the oxidizing capacity of lipids and act as antioxidants in renal disease. For instance, fluvastatin has been demonstrated to lessen oxidative stress in diabetic nephropathy and other renal disorders.[33-35] Fluvastatin was found to considerably diminish the accretion of advanced glycation end products and, to a lesser extent, the grade of fibrosis in the renal interstitial segment in further experiments conducted in animal models of ureteral obstruction.[35] In another study, fluvastatin was administered post-obstruction in a related trial, and the results showed a significant decrease in tubular epithelial apoptosis, extracellular matrix accumulation, and smooth muscle actin accumulation, along with a reduction in oxidative stress.

An assessment of vitamin E, N-acetylcysteine, and fluvastatin in the same study revealed that fluvastatin had the highest antioxidant potential and was also linked to altered extracellular signal-regulated kinase (ERK) activity over time.[36] Moreover, simvastatin therapy significantly reduced ventricular hypertrophy and fibrosis, which was linked to a decrease in ERK activity.[37] Consequently, statins may lessen oxidative stress and renal fibrosis through the control of specific mitogen-activated protein kinase (MAPK) pathways. Ischemia-reperfusion damage is the primary cause of acute kidney failure; individuals with this condition may also be at risk for chronic renal diseases in the future. Renal ischemia injury causes oxidative stress, which plays a role in apoptosis, among other regulated cell death mechanisms. During ischemia-reperfusion, blood flow to the renal parenchyma is initially markedly reduced and then restored, exacerbating oxidative damage.[38] Typically, 25% of the entire cardiac output reaches the highly metabolic kidneys, with the majority going to the renal cortex. In addition to conventional drugs, a non-steroidal mineralocorticoid receptor antagonist (finerenone) has recently been considered a cornerstone for cardiorenal protection, at least in part by reducing oxidative stress and inflammation. Although steroidal mineralocorticoid receptor antagonists, such as spironolactone, are well-known for their antioxidant effects, their use is limited by the risk of hyperkalemia. Conversely, finerenone has improved benefit-to-risk ratio as demonstrated in FIDELIO-DKD and FIGARO-DKD. These landmark studies demonstrated that finerenone significantly reduced the risk of CKD progression and cardiovascular events in patients with type 2 diabetes. This compound is an NADPH oxidase inhibitor, thereby reducing ROS directly. This, in turn, can disturb the vicious loop of oxidative stress, inflammation, and fibrosis in the kidney.[39-42]

Meanwhile, SGLT2 inhibitors have displayed significant cardiorenal benefits beyond their glucose-lowering effects. Trials such as DAPA-CKD and EMPA-KIDNEY revealed that these agents reduce the decline of kidney function across a wide spectrum of CKD, even in nondiabetic patients. The mechanisms are multifaceted, but an important factor is the mitigation of oxidative stress. SGLT2

inhibitors reduce mitochondrial dysfunction and ROS generation by optimizing tubular workload and mitigating oxygen deficiency. This is followed by downstream decreases in inflammasome activation and profibrotic signaling. The synergy observed when SGLT2 inhibitors are combined with finerenone has been evaluated (e.g., the CONFIDENCE trial) and suggests that targeting different pathways within the oxi-inflamm-aging axis may result in additive benefit.[42-44]

The renal medulla is physiologically hypoxic. Due to the presence of numerous active transporters and pumps, renal medullary cells are particularly vulnerable to further reductions in perfusion and oxygen tension. Depending on the sensitivity of the nephron segment, varying levels of necrosis and apoptosis are observed in these regions. The highest rates of cell death are induced by reperfusion of ischemic tissue[45] as a result of inflammation, as well as oxidative stress.[46] These processes are closely linked: many inflammatory mediators produce ROS, which in turn triggers an inflammatory response.[47]

Because their outer shells contain one or more unpaired electrons, ROS are extremely reactive. By reducing free radicals or using them to oxidize other chemical species and form covalent bonds, these electrons can be donated or lost. Several significant intracellular substrates, including phospholipids, DNA, enzymes, and various proteins, have been demonstrated to be oxidized by ROS.[48,49] These reactions can produce highly reactive metabolites, initiating a chain reaction that ultimately results in irreversible cell damage and death. Particularly, oxidized phospholipids have been shown to contribute to the pathogenesis of kidney diseases[50,51] and are involved in various cell death mechanisms, including ferroptosis. Moreover, ROS have been linked to the direct induction of apoptosis via promoting ceramide formation and the release of cytochrome c from the mitochondria.[52] A wealth of evidence suggests that impaired kidneys' antioxidant scavenging exacerbates renal injury. This condition may also serve as the underlying cause of some oxidant-related changes in age-related renal diseases.[53]

5. The role of oxidative stress in aging

Today, human life expectancy has significantly increased—surpassing 100 years and far exceeding that of our ancestors—as a result of advancements in medical care and living conditions. Studies on the aging process are a new field of research that encompasses diverse transcriptions and multiple signaling pathways.[54] Although the aging process occurs in almost all animal species, most do not experience it because they die before it occurs due to environmental factors, such as predation, starvation, disease, and other hazards.[55] However, senescence is a negligible phenomenon in the physiologic functions and reproductive system capability if there is no increase in age-related mortality rate.[56,57]

Animals such as the rough-eye rockfish, naked mole rats, and certain turtles, which exhibit lifespans over eight times longer than those of comparable species like mice, have gained significant attention. Morevati *et al.*[58] showed that the aging-suppressor gene *klotho* and the hepatic *klotho* pathways protect cells in naked mole rats, suggesting their role in the aging progression. Progress in understanding the processes involved in increasing the lifespan of these animal species provides a unique opportunity to comprehend the aging phenomenon and develop new strategies to address it. The cumulative harmful changes in cells and tissues result in aging, increasing susceptibility to disease and mortality. Numerous hypotheses have been suggested to explain the aging process.[59]

Aging is an irreversible process described by halted cell growth and the emergence of senescent cells. As cells age, they not only remain viable but also experience declines in functional abilities and deviations from normal morphology. During aging, transcriptional changes, delayed cellular repair, alterations in gene expression, modifications in protein synthesis, and shifts in growth factor levels are observed. The mammalian target of rapamycin is involved in the hypersecretory senescent phenotype observed.[60] The p53 protein, often referred to as the "guardian of the genome," is a tumor suppressor protein that plays a vital protective role against oxidative stress, DNA damage, and telomeric attrition. Additionally, in certain conditions, such as oxidative stress, inflammation, and DNA damage, premature cellular senescence might occur.[61]

Aging can induce an imbalance in ROS generation and antioxidant defense mechanisms. During the aging process, the functions of cells, tissues, and organs are impaired or lost. Oxidative stress occurs in aging-associated disorders, including CKD, cardiovascular disease (CVD), chronic obstructive pulmonary disease, cancer, neurodegenerative diseases, sarcopenia, and weakness.[62-64] Aging caused by oxidative stress and related disorders disrupts soft tissue function and homeostasis.[65,66]

Mitochondria, as a chief source of ROS and the powerhouse of cells, emerge as pivotal contributors to the pathogenesis of various human diseases and aging.[67,68] Their central role in aging is underscored by the widespread acceptance of mitochondrial dysfunction as a hallmark of aging and aging-related diseases.[69-72] Aging cells are prominently characterized by increased mitochondrial ROS levels, which oxidize proteins,

lipids, and mitochondrial DNA, thereby stimulating stress-response pathways. Simultaneously, there is a downregulation of mitochondrial DNA-encoded proteins, culminating in diminished mitochondrial respiration.[73,74] Increased ROS causes a diminution of scavenger enzyme activity, and this oxidative situation leads to the aging of cells.[75-77] Similarly, decreased levels of mitochondrial catalase and superoxide dismutase lead to oxidative stress, premature cellular aging, and other pathogenic conditions *in vivo* associated with aging.[78] Notably, interventions employing mitochondria-targeted ROS scavengers[79-82] and targeted overexpression of mitochondrial catalase[83,84] have demonstrated remarkable efficacy in extending lifespan in rodents. Elevated mitochondrial ROS levels, in conjunction with calcium ion (Ca^{2+}) accumulation and low mitochondrial membrane potential, prompt the opening of mitochondrial permeability transition (mPT) pores.[85-87] This cascade of events is particularly significant, as the opening of mPT pores has been linked to the acceleration of degenerative aging processes and aging-related diseases.[88-90] Furthermore, emerging research suggests a link between mPT pore opening and chronic renal failure,[91] highlighting the multifaceted role of mitochondrial dysfunction in both aging and disease progression.

Mitochondrial disturbances caused by oxidative stress reduce cellular lifespan, accelerate cellular aging, and impair the functional capacity of numerous biomolecules, such as enzymes and proteins.[78,92-94] Peroxidative damage to membrane lipids, along with a decrease in fatty acids and proteins, occurs. The junction near the endoplasmic reticulum and the mitochondria is called the mitochondria-associated membrane and has important physiologic and pathologic roles in cells. Aging is a complicated process that occurs alongside a series of changes in the organism, affecting cells, tissues, and organs. It impacts the function of cell sub-organelles. The aging process progressively weakens cells and tissues through oxidative stress, cumulative changes, DNA modifications, and disturbed proteostasis.

The turnover of cellular organelles is inefficient during aging[95] and intracellular organelles such as mitochondria and endoplasmic reticulum dynamically make temporary contacts known as mitochondria-associated membranes. These membranes have a unique molecular conformation and are specifically limited to interacting with membrane fragments. Molecular assemblies form junctions and create an exceptional local environment that can enhance the transfer of signals or cargo between different organelles. Mitochondria-associated membranes are involved in the pathogenesis of numerous age-related disorders.[96-98]

In addition to mitochondrial dysfunction, aging increases endoplasmic reticulum stress in cells. Mitochondrial contact with the endoplasmic reticulum plays a key role in the biogenesis of compartments that are derived from mitochondria.[99-101] These compartments possibly play a vital role in the adaptation of cells to environmental stresses.[101] Aging-related stress in the endoplasmic reticulum is associated with mitochondrial dysfunction.[101,102] In favor of this, spatial reorganization and changes in respiration, ATP levels, and Ca^{2+} uptake of mitochondria were associated with endoplasmic reticulum stress.[103,104] Endoplasmic reticulum stress causes a premature increase in mitochondrial metabolism and relies on Ca^{2+} transport and the joint function of these organelles.[103-106]

6. Chronic kidney disease: A premature aging of the kidney

The pathophysiology of CKD is comparable to that of normal aging; thus, it has been postulated that CKD contributes to the premature aging process concomitant with correlated diseases.[107] Moreover, distinct chronic diseases, including CVD, vascular calcification, inflammatory conditions, and mineral bone disorders, frequently occur in CKD patients.[108] CVD is considered the most clinically relevant comorbid condition related to CKD,[109,110] as CKD patients manifest a higher prevalence of non-conventional risk factors for cardiovascular problems. Also, several cardiovascular risk factors exacerbate the progression of CKD. In addition, it is well-known that CKD *per se* is a pivotal risk factor for CVD.[109] According to the United States Renal Data Systems, CKD patients experience a higher prevalence of acute myocardial infarction and heart failure.[109] In CKD patients undergoing dialysis, CVDs are the primary cause of mortality. Moreover, within the progression of CKD stages, CVD-related deaths show an increasing trend.[109]

There is an inverse relationship between cardiovascular mortality and glomerular filtration rate. However, the incidence of CVD is higher in patients receiving hemodialysis compared to those undergoing peritoneal dialysis.[109] Furthermore, kidney dysfunction and the consequent accumulation of uremic toxins result in a chronic inflammatory response and elevation of ROS, leading to the development of CVD. Senescence ultimately appears in injured endothelial cells.[111,112] It should be mentioned that endothelial disruption is the principal cause of CVD in CKD patients.[109] Stress signals induce premature senescence of endothelial cells in patients with kidney malfunction, an event that might induce the apoptotic machinery.[113] Additionally, damaged endothelial cells can express adhesive and coagulant molecules on

their surface, which in turn promote platelet binding, initiating coagulation, inflammation, and thrombosis, ultimately leading to cardiovascular events.[114] The presence of primary diseases, such as diabetes, hypertension, and hyperlipidemia, as well as factors including oxidative stress and inflammation, contributes to endothelial dysfunction during CKD.[115]

Hyperphosphatemia is another important complication detected in the majority of patients with kidney disorders, leading to increased ROS formation and decreased NO levels. Diminished NO levels, in turn, boost arterial rigidity and disturb the permeability of endothelial cells.[116-118]. NO synthesis is reduced in CKD patients since the activity of eNOS is inhibited. The activity of protein kinase C escalates ROS formation and inhibits eNOS expression.[119] Different signaling pathways have been implicated in uremic patients, including the endocrine phosphate-fibroblast growth factor-23-Klotho axis, the nuclear factor erythroid 2-related factor 2, and cascades related to the biogenesis of mitochondria and cellular senescence.[120] Oxidative stress is closely linked to the signaling pathways mentioned above. On the other hand, not only are multiple elements of oxidative stress observed in the early stages of CKD, but also a decrease in the function of key antioxidant enzymes, such as GSH peroxidase, has been detected in erythrocytes of uremic patients.[121,122] ROS interferes with metabolic pathways and alters cellular structure, leading to an inflammatory response during deteriorated renal function (Figure 2).

The AGEs, as biomarkers of senescence, can stimulate oxidative stress and its consequences via altering signaling pathways such as MAPK and NADPH oxidase 1–4.[123,124] The residue of AGEs derived from plasma proteins has been reported as a biomarker of mortality risk in renal diseases. Since the kidneys are the major site for the clearance of AGEs, they are reasonably susceptible to AGE-related

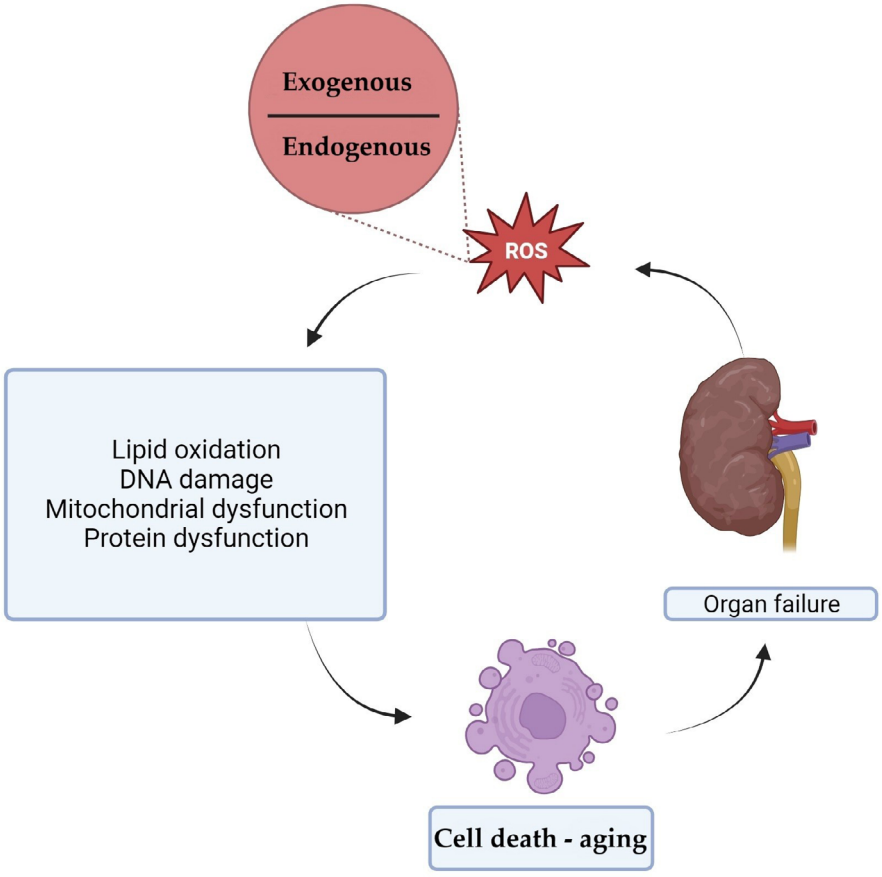

Figure 2. Vicious cycle of oxidative stress in the crosstalk between renal failure and aging. This figure presents a comprehensive model of the bidirectional relationship between CKD and accelerated aging. In this context, oxidative stress plays a pivotal role by affecting several cellular events. Figure created by authors using Microsoft powerpoint 2016.

injuries. The increase in circulating AGEs is highly linked with the risk of CKD. Moreover, patients with significantly decreased renal function exhibit an elevated AGE burden, particularly with uremia.[125,126] Given the close relationship between AGEs and oxidative stress, an antioxidant agent might also serve as a pharmacological inhibitor of AGEs, helpful in the treatment of CKD.[22,114]

The activation of the inflammatory system in CKD patients plays a crucial role in the pathogenesis of the disease. Uremic patients exhibit an imbalance between endogenous antioxidant and prooxidant factors. Additionally, increased nuclear internalization of the p65 subunit of nuclear factor-κB leads to elevated release of pro-inflammatory mediators and cytokines, as well as upregulation of various adhesion molecules.[127,128] It should be noted that the initial cellular event linking oxidative stress and inflammation to CKD is initiated by the activation of intra- and extracellular oxygen-derived radicals.[129] This activation further stimulates an inflammatory response due to kidney injury. These active radicals then readily react with the molecular constituents of the nephron, thereby producing secondary radicals.[130] As nephron injuries propagate, inflammatory activation increases free radical generation. This, in turn, leads to continued nephron damage during prolonged insults of recurrent oxidative stress and chronic inflammation.[131]

Although the normal inflammatory process tends to repair radical-associated injuries, the cyclical relationship between them can eventually result in further damage to the renal tissue.[132] Likewise, both inflammation and oxidative stress can become systemic, promoting injury to distal tissues.[133] In addition, the release of oxidizing components via activated pro-inflammatory immune cells triggers oxidative damage.[134] Antioxidants (gained by aerobic exercise and/or diet) have been shown to mitigate oxidative damage in these patients. Nevertheless, dietary restrictions in these patients limit adequate nutrient intake. Moreover, dialysis courses lead to the loss of vitamin C and selenium.[127,135,136] Vitamin K insufficiency is associated with a higher death risk in CKD patients in higher stages of the disease. Instead, physical activity might not be recommended despite its role in scavenging radicals and diminishing lipid peroxidation.[137]

The association between chronic inflammatory response and aging has resulted in the genesis of the term "inflamm-aging."[138] The relationship between free radicals and mitochondrial stress in the process of aging is a well-known theory that is gathered with immunosenescence formulas of the hypothesis of "oxi-inflame-aging."[139,140] Body systems responsible for homeostasis are mostly affected during chronic stress. Disturbances, including oxidative stress, prompt a reaction in activating the hemodynamic systems to remove the hazard. Conversely, injured homeostatic systems due to CKD do not alleviate the corresponding disruption; instead, they worsen it.[140,141] In that instance, inflammation leads to immunosenescence, which disrupts the other homeostatic systems by further increasing inflammation and oxidative stress, resulting in frailty and loss of adaptability.[142,143] Additionally, diminished renal function can likewise exacerbate inflammation.[142] In CKD patients, the retention of AGEs[141], and oxidation of proteins and pro-oxidant molecules[126,144], provide a pro-inflammatory niche.

Another pivotal cause of aging has been postulated to be closely linked to mutations and DNA damage that can alter DNA structure and produce dysfunctional proteins.[145] Hutchinson–Gilford progeria and Werner syndromes, as rare progeroid syndromes, show similar clinical manifestations as accelerated aging, in which defects in DNA repair play a critical role in the development of aged phenotype.[146] Unrepaired cytotoxic DNA injuries were shown to activate a highly conserved metabolic response to the insulin-like growth factor-1/insulin signaling, which repurposes resources from growing to life extension.[147] In the theory of aging linked with mitochondria and free radicals, where the commencement of aging is associated with the initiation of free radical reactions, it might be explained why females live longer than males.

Intriguingly, men are exposed to higher levels of mitochondria-related oxidative stress than females. High estrogen levels in females protect them against aging by increasing the expression of ROS-scavenging, longevity-associated genes.[148] Since the impaired function of mitochondria is a key event in aging and escalates the incidence of age-related diseases, mitochondrial deterioration might be involved in the mounting burden of CKD in the aged community.[149] As augmented oxidative stress of DNA is an indicator of uremia[150] and appears to be interconnected with several aspects of the aged phenotype, including atherosclerosis,[151] a malfunctioning response to cellular DNA injury may amass over time and stimulate premature aging. Mutations in genomic stability genes have recently been revealed to link a DNA damage response to progressive loss of renal function.[152] Table 1 summarizes the key pathological cascade involved in CKD-associated premature aging.

Table 1. Key pathological pathways in chronic kidney disease-associated premature aging: Mechanisms, manifestations, and therapeutic insights

Pathway/process	Key molecular mediators	Clinical and pathological links	Potential interventions
Mitochondrial dysfunction and ROS production	mtROS, ↓SOD2, ↓catalase, altered MAMs, mPT pore opening[63,74,81,88,100]	Energy deprivation, augmented cellular aging, fibrosis, and diminished organ function[63,69,74,148]	Targeting mitochondrial antioxidants,[75–77] lifestyle[136]
"Inflamm-aging" and immunosenescence	↑IL-6, ↑TNF-α, NF-κB activation, NLRP3 inflammasome, SASP[56,126,137,138]	Weakness, increased infection risk, and systemic inflammation[137,141,142]	Senolytics (e.g., dasatinib + quercetin) to clear senescent cells[153]
Premature endothelial senescence and vascular dysfunction	Uremic toxins, ↑p53/p21, ↓NO, ADMA, eNOS uncoupling[108,110,112,115,118]	Atherosclerosis, vascular stiffness, hypertension, and cardiovascular mortality[108,114,115]	ACE inhibitors/ARBs (e.g., enalapril, losartan),[30,31] statins (e.g., fluvastatin)[32–34]
Fibrotic signaling and tissue senescence	TGF-β, ↑fibronectin, ↑collagen, SASP secretion, fibroblast activation[56,110]	Glomerulosclerosis, tubulointerstitial fibrosis, and progressive eGFR decline[1,2]	AT1 receptor antagonists,[30,31] statins (e.g., fluvastatin)[34,35]
AGE–RAGE axis activation	AGEs, RAGE, MAPK, NADPH oxidase (NOX1–4)[11,21,122,123]	Vascular complications, increased oxidative stress, inflammation, and higher mortality risk[11,21,124,125]	Antioxidants as potential AGE inhibitors,[21,113] dietary control[125]
Dysregulated DNA repair and genomic instability	Impaired DNA repair (e.g., FAN1), ↑p53, telomeric attrition[57,144,145,149,151]	Genomic instability, accelerated cellular aging, increased cancer risk, and atherosclerosis[145,149,150]	Modulation of IGF-1/ insulin signaling pathway[146]

Notes: ↑Increased; ↓Decreased. Abbreviations: ACE: Angiotensin-converting enzyme; ADMA: Asymmetric dimethylarginine; AGE: Advanced glycation end-product; ARB: Angiotensin II receptor blocker; AT1: Angiotensin II Type 1 receptor; eGFR: Estimated glomerular filtration rate; eNOS: Endothelial nitric oxide synthase; FAN1: Fanconi-associated nuclease 1; IGF: Insulin-like growth factor; IL: Interleukin; MAMs: Mitochondria-associated membranes; MAPK: Mitogen-activated protein kinase; mPT: Mitochondrial permeability transition; mtROS: Mitochondrial reactive oxygen species; NADPH: Nicotinamide adenine dinucleotide phosphate; NF: Nuclear factor; NLRP3: Nucleotide-binding oligomerization domain-, leucine-rich repeat-, and pyrin domain-containing protein 3; NO: Nitric oxide; NOX: Nicotinamide adenine dinucleotide phosphate oxidase; RAGE: Receptor for advanced glycation end-product; ROS: Reactive oxygen species; SASP: Senescence-associated secretory phenotype; SOD2: Superoxide dismutase 2; TGF: Transforming growth factor; TNF: Tumor necrosis factor.

7. Conclusion

In summary, this review has critically synthesized the evidence on the bidirectional interplay between oxidative stress and aging as a central pathogenic driver in CKD. CKD progression is markedly accelerated by a self-reinforcing cycle in which mitochondrial dysfunction serves as a primary hub for ROS production. This promotes chronic inflammation and premature cellular senescence, a condition aptly termed "oxi-inflamm-aging." An important vision arising from this analysis is the critical distinction between therapeutic strategies that merely scavenge oxidative damage downstream compared to those that target its upstream sources. The consistent failure of broad-spectrum antioxidant regimens stands in striking contrast to the clinical success of agents such as SGLT2 inhibitors and finerenone, whose benefits appear to derive from their ability to modulate fundamental metabolic and pro-fibrotic pathways underlying pathological oxidant production.

Currently, a focused effort to identify and validate clinically usable biomarkers of biological aging is urgently

required. This will not only help identify high-risk patients but also enable accurate measurement of the effectiveness of potential anti-aging therapies.

However, translating antioxidant therapy from bench to bedside in CKD faces several challenges. Non-specific scavengers fail to treat patients, demonstrating the complexity of redox biology. Future approaches might involve mitochondria-targeted antioxidants or targeting upstream drivers of ROS, as with SGLT2 inhibitors. While lifestyle modifications are promising for accelerating endogenous antioxidant defenses, their application in progressive CKD is often inadequate due to the presence of comorbidities. Therefore, future exploration should implement personalized tactics that recognize patient subgroups most likely to benefit from distinct redox-modulating treatments.

Acknowledgments

None.

Funding

This study was funded by the Kidney Research Center, Tabriz University of Medical Sciences, Iran (Grant number: 73083).

Conflict of interest

Rovshan Khalilov is an Editorial Board Member of this journal, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

Conceptualization: All authors
Writing – original draft: All authors
Writing – review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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