Pediatric Nephrology
https://doi.org/10.1007/s00467-018-4005-4

REVIEW

Oxidative stress in chronic kidney disease

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Received: 21 December 2017 / Revised: 3 June 2018 / Accepted: 14 June 2018

Abstract

Oxidative stress (OS), defined as disturbances in the pro-/antioxidant balance, is harmful to cells due to the excessive generation of highly reactive oxygen (ROS) and nitrogen (RNS) species. When the balance is not disturbed, OS has a role in physiological adaptations and signal transduction. However, an excessive amount of ROS and RNS results in the oxidation of biological molecules such as lipids, proteins, and DNA. Oxidative stress has been reported in kidney disease, due to both antioxidant depletions as well as increased ROS production. The kidney is a highly metabolic organ, rich in oxidation reactions in mitochondria, which makes it vulnerable to damage caused by OS, and several studies have shown that OS can accelerate kidney disease progression. Also, in patients at advanced stages of chronic kidney disease (CKD), increased OS is associated with complications such as hypertension, atherosclerosis, inflammation, and anemia. In this review, we aim to describe OS and its influence on CKD progression and its complications. We also discuss the potential role of various antioxidants and pharmacological agents, which may represent potential therapeutic targets to reduce OS in both pediatric and adult CKD patients.

Keywords Oxidative stress · Antioxidants · Chronic kidney disease · Cardiovascular disease

Abbreviations

ADMA	Asymmetric dimethylarginine
ARE	Antioxidant response element
CVD	Cardiovascular disease
CKD	Chronic kidney disease
eNOS	Endothelium nitric oxide synthase
GSH	Glutathione
GSH-PX	Glutathione peroxidase
H_2O_2	Hydrogen peroxide
HO-1	Heme oxygenase-1
IS	Indoxyl sulfate
MPO	Myeloperoxidase
NADPH	Reduced nicotinamide adenine dinucleotide phosphate

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00467-018-4005-4) contains supplementary material, which is available to authorized users.

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Published online: 13 August 2018

NO	Nitric oxide
NOX	NADPH oxidase
NQO1	NADPH quinone oxidoreductase
Nrf2	Nuclear factor erythroid 2-related factor 2
$O_2^{\bullet-}$	Superoxide anion
OS	Oxidative stress
OxLDL	Oxidized low-density lipoproteins
ROS	Reactive oxygen species
SDMA	Symmetric dimethylarginine
Se	Selenium
SOD	Superoxide dismutase
XO	Xanthine oxidase
XDH	Xanthine dehydrogenase

Introduction

Oxidative stress (OS) is defined as a state of imbalance between excessive oxidant (free) radicals and insufficient degradation of those radicals by antioxidant systems as an in-house defense mechanism (Fig. 1). Oxidant compounds such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) are formed under physiological conditions and are removed by several antioxidant defense mechanisms [1, 2]. Reactive species are not necessarily harmful to the cells. At moderate concentrations, Reactive oxygen species/reactive nitrogen species act as second messengers and regulate intracellular signal transduction pathways. In case of an imbalance in the prooxidant/antioxidant equilibrium, OS is created which leads to metabolic dysregulation and/or oxidation end products of lipids, DNA, and proteins and/or oxidative damage in cells, tissues, or organs, caused by ROS/RNS [1, 2]. Ultimately, this results in several disorders due to the inactivation of cellular molecules [3].

The kidney is a highly energetic organ. This makes it more vulnerable to damage caused by OS [4, 5]. In turn, OS is associated with kidney disease progression [6, 7]. Furthermore, several complications of chronic kidney disease (CKD) such as inflammation and cardiovascular disease (CVD), the major cause of death in patients with CKD, are also linked to increased levels of OS. The 'oxidative' link between CKD and its complications is achieved through several mechanisms, such as uremic toxin-induced endothelial nitric oxide synthase (eNOS) uncoupling [8] and increased nicotinamide adenine dinucleotide phosphate-oxidases [NADPH oxidases (NOX)] activity [9, 10], but also antioxidant losses due to dietary restrictions, diuretics use, protein energy wasting, and/or decreased intestinal absorption [11, 12].

In the current review, we will discuss the nature, source, and consequences of increased OS and decreased antioxidative capacity in CKD.

Sources of increased oxidative stress

Reactive oxygen species and reactive nitrogen speciesrepresent a class of reactive molecules which are continuously formed by oxidation reactions in living cells during normal metabolic processes by both enzymatic and nonenzymatic reactions. Free, or

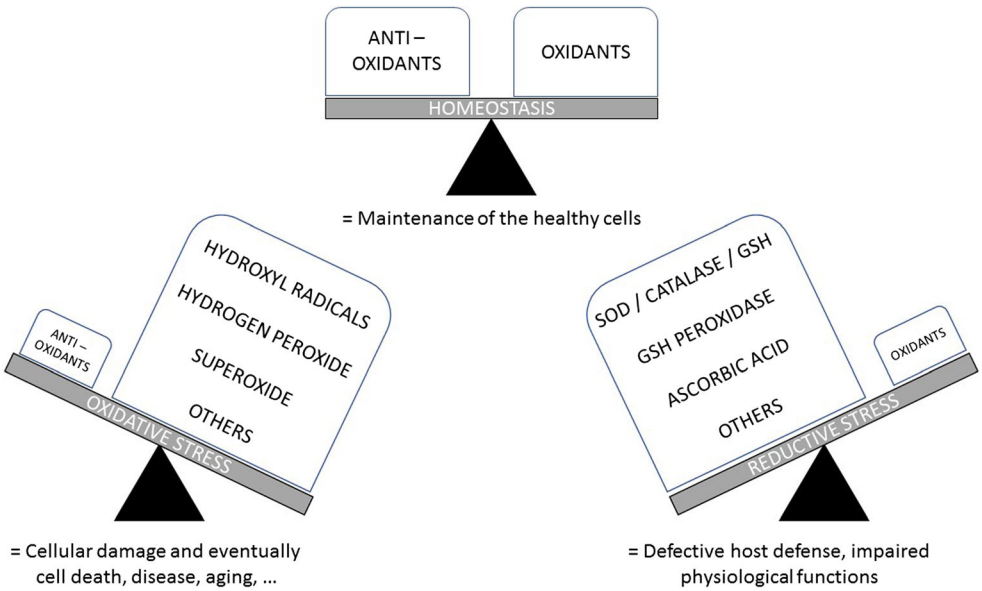

Fig. 1 Imbalance between oxidants and antioxidants. To maintain cellular homeostasis, a balance is necessary between the production and degradation of reactive oxygen species (ROS). Oxidative stress is a state of imbalance between excessive oxidant formation and the degradation of those radicals by antioxidants. Metabolic dysregulation resulting in severe cell damage, cell death, aging, and disease can be a consequence of the oxidative stress. On the other hand, an excessive production of antioxidants (such as glutathione (GSH), superoxide dismutase (SOD), catalase, ascorbic acid, α-tocopherol, …) is also harmful to the cell. 'Reductive stress' causes a defective host defense and an impaired physiological signaling

primary, radicals, defined as independent chemical species with one or more unpaired electrons, are highly reactive in search for another unpaired electron. Examples are hydroxyl ($OH^{\bullet}$) and the less reactive superoxide anion ($O_2^{\bullet-}$), nitric oxide radicals ($NO^{\bullet}$), and nitrogen dioxide radicals ($NO_2^{\bullet}$). When two unpaired electrons react with each other to form a covalent bond, a new nonradical molecule is formed. More often, however, free radicals attack nonradical molecules resulting in a new (secondary) radical molecule, initiating as such a chain reaction. This chain reaction of primary and secondary radicals eventually leads to oxidative damage of several tissues and organs [13]. Examples of secondary radicals are hydrogen peroxide (H_2O_2), ozone (O_3), singlet oxygen ($^1O_2$), hypochlorous acid (HClO), nitrous acid (HNO_2), dinitrogen trioxide (N_2O_3), peroxynitrite ($ONOO^-$), and lipid peroxides (Fig. 2) [13].

Since ROS are unstable and have a short half-life, it is difficult to measure the amount of circulating free radicals. Several oxidation end products are therefore used to assess the redox state: These are end products of lipid peroxidation, DNA damage, or the oxidation of proteins and amino acids [14] (Supplementary Table 1).

Sources of oxidative stress

Endogenous sources

Normal metabolic processes in aerobic conditions constitute a major source of ROS. In living organisms, ROS are generated as products of biochemical reactions in the plasma membrane, cytoplasm, peroxisomes, lysosomes, and on the membranes of mitochondria and endoplasmic reticulum. The mitochondria, together with nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase (XO), myeloperoxidase (MPO), and the eNOS, are the major source of ROS formation. Other enzyme sources are prostaglandin synthase, lipoxygenase, and flavoprotein dehydrogenase [3, 15].

Mitochondrial electron-transport chain Along the mitochondrial electron-transport chain, electrons are transferred to reduce oxygen to water and produce ATP by oxidative phosphorylation of the reduced forms of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$). At complexes I and III of the electron-transport

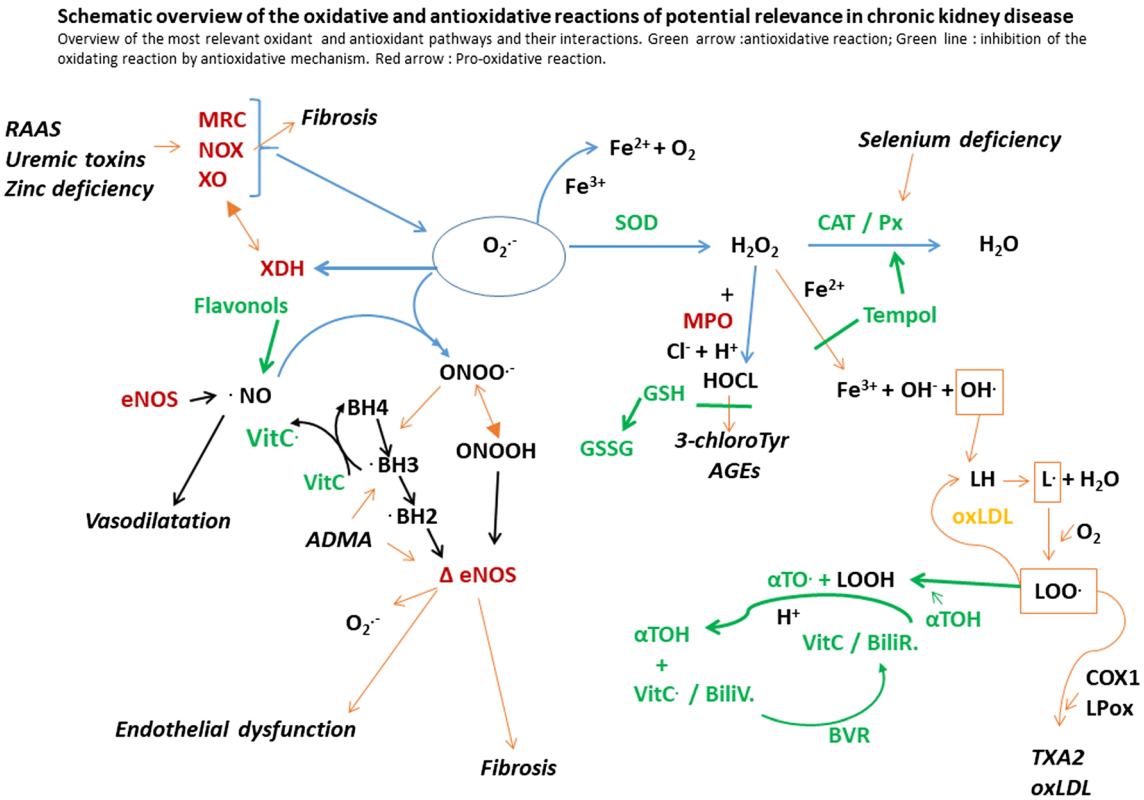

Fig. 2 Mechanisms of oxidative cellular damage and the antioxidant defense. Overview of the most relevant oxidant and antioxidant pathways and their interactions. Green arrow: antioxidative reaction; green line: inhibition of the oxidating reaction by antioxidative mechanism; red arrow: pro-oxidative reaction. Abbreviations: αTOH, alpha tocopherol; ADMA, asymmetric dimethylarginine; AGEs, advanced glycation end products; BH4, (6R)-5,6,7,8-tetrahydro-l-biopterin; BiliR, bilirubin; biliV, biliverdin; BVR, biliverdin reductase; Cat, catalase; COX, cyclooxygenase; eNOS, endothelial NO synthase; Δ eNOS, eNOS uncoupling; Fe^{2+}, iron; GSH/GSSH, glutathione; H_2O_2, hydrogen peroxide; HOCL, hypochlorous acid; LOOH, fatty acid chain; LOO^-, lipid peroxyl radical; MPO, myeloperoxidase; MRC, mitochondrial respiratory complex; NOX, NADPH oxidase; NO, nitric oxide; ONOO, peroxynitrite; O_2, oxygen; $O_2^{\bullet-}$, superoxide anion; PX, peroxidase; SOD, superoxide dismutase; TXA, thromboxane; VitC, vitamin C; XDH, xanthine dehydrogenase; XO, xanthine oxidase

chain, respectively, NADH dehydrogenase and ubiquinone-cytochrome bc1, $O_2^{\bullet-}$ is generated due to incomplete reductions and electrons that leak away from the main path and directly reduce oxygen molecules to ROS, such as $O_2^{\bullet-}$, H_2O_2, and $OH^{\bullet}$ [15, 16].

NADPH oxidases The family of NADPH oxidases consists of seven members: five different types of NADPH oxidases (NOX) and two dual oxidases (DUOX1–2), DUOX1. All five of the NOX enzymes consist of two heme containing transmembrane oxidoreductases that span the membrane six times as α-helices with cytosolic N- and C-termini. The classic NADPH oxidase is gp91phox, also called Nox2. NOX catalyzes the transfer of electrons from the cytosol to the extracellular space or within specialized compartments of the cell. NADH or NADPH, present in the cytosol, is the electron donor for the 1-electron reduction of oxygen by the NOX [17, 18]. The different isoforms differ in Nox-binding proteins, both tissue distribution and intracellular localization and regulation. NOX1 and NOX4 have been shown to be key players across a broad range of diseases [19]. In both the kidney and the vasculature, NADPH oxidase 4 (NOX4) is the most important isoform, located in renal tubules, renal fibroblasts, glomerular mesangial cells, and podocytes in the kidney and in the membrane of mainly endothelial cells and fibroblasts in the vasculature. In normal conditions, NOX have a low basal activity, but they can be triggered by cytokines, growth factors, hyperlipidemia, and high glucose [20]. The generation of ROS, such as H_2O_2, by NOXs can trigger the activation of several other prooxidative enzymes, thus leading to a vicious cycle of redox dysfunction [21].

Endothelial nitric oxide synthase Different vital functions, such as neurotransmission and vascular tone, are regulated by NO. In mammals, three different isoforms of NO synthases (NOS) can be found: neuronal NOS (nNOS), inducible NOS (iNOS), and eNOS [22]. L-arginine is metabolized by NOS to form L-citrulline and NO, with NADPH and oxygen serving as co-substrates. To work properly, NOS need the pteridine cofactor tetrahydrobiopterin (BH4) [23]. In blood vessels, eNOS is the most abundant of the NOS isoforms and the NO synthesized in the endothelium is an important protective molecule of the vasculature. Under pathological conditions, eNOS can produce ROS by itself, which is called 'eNOS uncoupling': Electron transfer within the active site is uncoupled from L-arginine oxidation and oxygen is reduced to form $O_2^{\bullet-}$ [23]. Superoxide anion then combines rapidly with NO to generate peroxynitrite ($ONOO^-$). Several mechanisms can cause eNOS uncoupling: for example, deficiency in BH4 or in L-arginine and the accumulation of asymmetric dimethylarginine (ADMA), a naturally occurring L-arginine analogue and endogenous NOS inhibitor. ROS itself can perpetuate eNOS uncoupling by oxidation reactions on either BH4 and protein arginine N-methyltransferase (PRMT type 1) or demethylarginine dimethylaminohydrolase (DDAH), leading to increasing levels of ADMA.

Myeloperoxidase MPO, a heme-containing peroxidase that is synthesized during myeloid differentiation, is abundantly stored in azurophilic granules of leukocytes. Normally, MPO catalyzes the formation of HClO from the H_2O_2-mediated oxidation of halide ions [24]. However, in various diseases, degranulation leads to the release of MPO into the extracellular space, where it can oxidize not only halide ions but also other substrates to mediate tissue damage [25]. Myeloperoxidase has a well-known role in atherosclerosis. For example, it contributes to oxidative modification of low density lipoprotein (LDL) by catalyzing lipid peroxidation [26]. Clinical trials have demonstrated a correlation of circulating MPO levels and MPO-derived oxidized molecules with coronary artery disease (CAD) and clinical events [27, 28].

Xanthine oxidases Xanthine oxidoreductase acts both as a xanthine dehydrogenase (XDH) and XO, which are both single gene products. XDH as well as XO are associated with the terminal two steps of purine degradation in humans: hypoxanthine–xanthine–uric acid. Under physiological conditions, XDH uses hypoxanthine or xanthine as a substrate and NAD^+ as a cofactor to produce uric acid and NADH. Nevertheless, under inflammatory conditions, posttranslational modification due to the oxidation of the cysteine residues converts XDH to XO, which has an increased affinity for oxygen as a cofactor to finally produce uric acid and $O_2^{\bullet-}$ or H_2O_2 [29].

Nonenzymatic, exogenous, and environmental sources

Air and water pollution, cigarette smoke, alcohol, heavy or transition metals, drugs, industrial solvents, and radiation are the main environmental causes of OS. Those agents can enter the body through different pathways and eventually get metabolized into free radicals [30]. Free transition metals like copper and iron, in the presence of hydroperoxides, are strong catalysts for oxidation reactions. They can initiate lipid peroxidation by cleavage of LOOH to lipid alkoxyl radicals. Their exact role in disease and atherosclerosis remains controversial. Copper is transported by albumin to the liver where it is incorporated in ceruloplasmin for transport to various tissues. Ceruloplasmin has ferroxidase capacity required for iron incorporation into ferritin [31]. It has also been reported to induce and facilitate LDL oxidation by free metals [32, 33].

Antioxidants

The human body has a built-in defense mechanism against OS: the antioxidants. Antioxidants inhibit several destructive

oxidation reactions by being oxidized themselves. This defense system operates through a cascade of blocking the initial production of free radicals and scavenging oxidants, in which the oxidants are converted to less toxic compounds and the secondary production of toxic metabolites is blocked (Fig. 2). Subsequently, the defense system aims to repair the molecular injury or enhance the endogenous antioxidant defense system, which is composed of enzymatic and nonenzymatic antioxidants.

Enzymatic antioxidants

The enzymatic antioxidants can be divided in two groups: (i) primary or constitutively acting antioxidant enzymes (superoxide dismutase (SOD), catalase, glutathione (GSH) peroxidase, and thioredoxin), that function to maintain the reducing tone within cells and keep the redox balance stable, and (ii) the antioxidant response element (ARE)-driven enzymes: phase 2 genes encode for enzymes that directly inactivate oxidants, increase levels of GSH synthesis and regeneration, and stimulate NADPH synthesis in times of inflammation or stress. They are regulated by upstream AREs which are first activated by the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) [34, 35]. Heme oxygenase-1 (HO-1) and NADPH quinone oxidoreductase (NQO-1) belong to the ARE-driven enzymes.

Primary enzymatic antioxidants

Superoxide dismutase SOD is a key enzyme in the detoxification of free radicals in the cell. It converts $O_2^{\bullet -}$ to H_2O_2 and oxygen, and in turn, catalase or the glutathione peroxidase system reduces H_2O_2 to water. Superoxide dismutase also plays a role in inhibiting the oxidative inactivation of NO. Mammalian tissues contain three types of SOD: copper-zinc-containing SOD, manganese-containing SOD, and the extracellular SOD, which are expressed in the cytosol, mitochondrial matrix, and extracellular space, respectively.

Catalases and peroxidases Two enzymes metabolize H_2O_2 resulting from SOD or generated by, among others, xanthine oxidase. Catalase (CAT) directly decomposes H_2O_2 to water and O_2, whereas the peroxidases (PX) use H_2O_2 to oxidize another substrate, such as GSH. Mostly, the GSH-PXs cooperate with CAT for the decomposition of H_2O_2 to H_2O and oxidized glutathione (GSSG), which is then reduced by glutathione reductase. GSH-PX requires GSH as a hydrogen donor to decompose H_2O_2 to water and oxygen and selenium (Se) as a cofactor to participate in the reaction with peroxides [15, 36].

Antioxidant response element-driven enzymes

Heme oxygenase-1 HO-1 is an inducible stress-responsive enzyme responsible for the rate-limiting enzymatic degradation of heme to free ferrous iron, carbon monoxide (CO), and biliverdin [37], the latter being rapidly converted by biliverdin reductase to bilirubin. Each of these enzymatic end products exerts antioxidative, anti-inflammatory, and anti-apoptotic effects through different mechanisms [38, 39]. Being an early stress-responsive protein, HO-1 can be induced by a variety of agents that cause OS. The protective properties of HO-1 have been extensively studied in in vitro and animal models of atherosclerosis, ischemia-reperfusion injury, and acute kidney injury [40–42]. The activity of HO-1 is influenced by genetic factors. A (GT)n dinucleotide repeat polymorphism in the promoter region of HO-1 has been extensively studied and shorter (GT)n repeats have been found to result in a higher HO-1 expression and activity.

Nonenzymatic antioxidants

The nonenzymatic antioxidants, or low molecular weight antioxidants, are found in the plasma, extracellular fluids, intracellular fluids, lipoproteins, and membranes. Besides GSH, this group contains several dietary antioxidants as well as compounds synthesized in the body, which can be further divided in two subgroups: the water-soluble antioxidants and the lipid-soluble antioxidants.

Glutathione

The major soluble nonenzymatic antioxidant is GSH, which is dependent on the glutathione peroxidase activity. It is highly abundant in all cell compartments and it is endogenously synthesized throughout the body. This antioxidant protects cellular macromolecules, such as proteins and membrane lipids, against ROS. The detoxification of H_2O_2 and lipid peroxides is one of its actions. Because of the free thiol group, it can donate an electron to the radicals to make them harmless. The donation causes the oxidation of the antioxidant itself, which turns it into glutathione disulfide (GSSG). In turn, the latter is reduced back to GSH by the enzyme glutathione reductase, which uses NAD(P)H oxidase as the electron donor [43]. To properly maintain the oxidative balance in the cell, it is necessary for the cell to contain high levels of GSH and low levels of GSSG.

Dietary antioxidants and compounds synthesized in the body

(i) Water-soluble antioxidants

Water-soluble antioxidants mainly react with oxidants in the cytosol and plasma. Again, in this group, a distinction

can be made between dietary antioxidants, which include ascorbic acid and polyphenols and endogenous antioxidants, which include albumin and bilirubin [15, 44, 45].

(1) Water-soluble dietary antioxidants

Ascorbic acid Ascorbic acid, or vitamin C, is a reducing agent with both intracellular and extracellular antioxidant capacities [15]. Ascorbic acid is subsequently oxidized to semidehydroascorbic acid and dehydroascorbic acid. Both semidehydroascorbic acid and dehydroascorbic acid can be reduced to ascorbic acid by three different pathways as well as by GSH [46].

Polyphenols—flavonoids The most abundant dietary antioxidants are the plant-derived polyphenols such as cocoa flavonols and resveratrol. Fruits, vegetables, and chocolate are some of their sources. The most studied group is the flavonoids, responsible for the colors of flowers, leaves, and fruits. The chemical structure of flavonoids contains two aromatic rings, which are bound to each other by three carbon atoms to form an oxygenated heterocycle. Several studies showed that a polyphenolic-rich diet reduces the risk for chronic diseases [47]. Since the phenolic groups are excellent hydrogen donors, they trap radicals and interrupt oxidation chain reactions in the cell. By donating a hydrogen, the phenolic group forms a stable phenoxyl radical, which is stabilized by a resonance effect [47]. Recently, beneficial effects of cocoa flavonols on endothelial dysfunction and blood pressure have been demonstrated [48].

(2) Water-soluble endogenous antioxidants

Albumin and bilirubin Human serum albumin, synthesized in the liver, is an abundant protein present in the plasma. It has several functions, which goes from transporting metals, fatty acids, and drugs in the blood to the regulation of osmotic pressure and the distribution of fluids between different compartments. Since albumin can bind many types of molecules, it has a good antioxidant capacity. For example, albumin binds metal ions, especially copper and iron, to prevent the formation of hydroxyl radicals by the Fenton reaction. On the other hand, albumin can also bind circulating bilirubin with a high affinity. This albumin-bilirubin complex is found to be an inhibitor of lipid peroxidation, and it was shown that bound bilirubin protects α-tocopherol from damage mediated by peroxyl radicals. Albumin also contains the largest source of extracellular thiols, since it has a reduced cysteine residue. Such a thiol source makes it possible to scavenge hydroxyl radicals and HOCl [49].

(ii) Lipid-soluble antioxidants

Lipid-soluble antioxidants are mainly located in the plasma membranes and lipoproteins and protect cell membranes from lipid peroxidation. This group contains (among others) α-tocopherol, β-carotene, and coenzyme Q10.

α-Tocopherol The lipid-soluble vitamin E mainly refers to α-tocopherol, which is the most active form of eight different tocopherols. It acts as a defense against oxidant-induced membrane injury. Once α-tocopherol reacts with an oxidant, especially peroxyl radicals, it converts to α-tocopherol free radicals (α-TO•), which are relatively nonreactive. These radicals, in turn, can react with other free radicals to form a nonreactive radical product. The remaining α-tocopherol free radicals need ascorbic acid to reduce them back to α-tocopherol [15].

(iii) Trace elements zinc and selenium

Both zinc and selenium are essential trace elements involved in several biochemical processes in the human body. Zinc is an important cofactor of SOD, as discussed earlier, and it is also required for the upregulation of the zinc-finger protein A20, which inhibits inflammatory pathways through the inhibition of TNFα and IL1β [50]. Zinc deficiency was shown to increase OS and induce cyclooxygenase-2 (COX-2) and E-selectin gene expression, as well as monocyte adhesion in cultured endothelial cells, suggesting a key role in inflammatory diseases such as atherosclerosis [50, 51]. Selenium mainly functions as an antioxidant in the form of the selenoproteins. At least 30 selenoproteins have been identified, including GSH-PX, selenoprotein P, thioredoxin reductase, and selenophosphate synthetase [52]. Girelli et al. also found an association between Se levels and CVD [53].

Oxidative stress in the progression of kidney disease (Table 1)

The contribution of OS to the progression of kidney disease and subsequent renal function loss has been extensively studied [6, 45]. ROS play an important role in the physiological regulation of kidney function which consequently makes the kidney especially vulnerable to redox imbalances and oxidative stress. Formation of ROS or changes in ROS production can occur both in the renal cortex and medulla, with a broad range in effects, going from alteration in renal blood flow over sodium/fluid retention to inflammation and fibrotic changes and onset of proteinuria [89].

There is plenty of evidence for increasing levels of OS markers with deteriorating renal function, beginning from early CKD stages [11] in both adults and children. Like in adults, data from children and young adults with CKD show

Table 1 Evidence of disturbed oxidative/antioxidative balance in CKD, CKD progression, and CKD-CVD in humans

Mechanism of increased oxidative stress or decreased antioxidative capacity	Evidence for its disturbance in CKD	Impact on renal disease (I) and evidence from interventional studies (E)	Impact on CVD in CKD (I) and evidence from interventional studies (E)
Mitochondrial respiration	* Increased mitochondrial ROS generation [54, 55] * Mitochondrial dysfunction [56, 57]	(I) * Influence on cyst growth in ADPKD [58] * MiRNAs and renal fibrosis [59] (E) RAAS blockade (eGFR, Alb) [60, 61]	(I) No data available (E) No data available
NAPDH oxidases	Increased NOX4 activity caused by uremic toxins [9, 62], zinc deficiency [63], and RAAS	(I) * RAAS [64] * Zinc deficiency [63] (E) NOX Inhibitor GKT137831 (Alb) [19]	(I) * RAAS [65] * Uremic toxins IS, AGEs [66, 67] (E) No data available
eNOS	eNOS uncoupling caused by uremic toxins [68], ADMA [69, 70]	(I) No data available (E) No data available	(I) ADMA mediated increased endothelial dysfunction and CVD [70] (E) No data available
Myeloperoxidase	Positive correlation between 8-iso-PGF2α levels with serum MPO levels [71]	(I) No data available (E) No data available	(I) MPO and CVD in CKD [72] (E) No data available
Xanthine oxidases	Increased XO activity in CKD [73]	(I) No data available (E) XO Inhibitors and renal function (eGFR) [74]	(I) XO and CVD in CKD [73] (E) No data available
Lipid peroxidation	IV iron-induced OS [75]	(I) No data available (E) No data available	(I) * Iron-induced OS and early atherogenesis [75] * Ceruloplasmin and CVD events [76] (E) No data available
SOD, peroxidases, GSH	* Decreased SOD [11] * GSH depletion [77] * Selenium deficiency [78]	(I) No data available (E) Selenium supplementation (eGFR) [52, 79]	(I) No data available (E) No data available
Heme oxygenase-1	No data available	(I) HO-1 $(GT)_n$ repeat polymorphism and renal function in ADPKD, TX, IgA nephropathy [80] (E) No data available	(I) HO-1 $(GT)_n$ repeat polymorphism and CVD [81] (E) No data available
Nonenzymatic antioxidants	* Hypoalbuminemia [82] * Deficiency in trace elements: * Selenium deficiency [78] * Zinc deficiency [63]	(I) No data available (E) Zinc supplementation (Alb) [83, 84]	(I) * Hypoalbuminemia and increased CVD events [85] * Hypovitaminosis C [86] (E) * Tocopherol supplementation and CVD events [87] * Cocoa flavonol and endothelial dysfunction in ESRD [88]

increasing concentrations of OS markers such as mitochondrial superoxide and oxidized LDL [90–92], homocysteine [93], as well as a deficiency of SOD and GSH [91, 92] together with disease progression. Also, several uremic toxins, associated with increased OS in CKD, increase with worsening renal function, such as the retention solute IS [94], F_2-isoprostanes, MDA, and ADMA [95, 96]. However, these findings do not imply necessarily a causal role for OS in renal function loss [11]. Some end products of OS-induced lipid peroxidation have been shown to be more than just oxidation markers in CKD: Malondialdehyde is the product of polyunsaturated fatty acid peroxidation. It has been shown to induce dysfunctional high-density lipoproteins (HDL) molecules [97] and contribute to increased cardiovascular morbidity [98]. There are several, albeit mainly preclinical, studies showing mechanistic evidence for a causative role for increased OS in CKD progression. The most elaborated is undoubtedly the role of OS in diabetic nephropathy. In this specific context, increased OS has been shown to be due to multiple mechanisms including mitochondrial dysfunction, increased NOX activity, eNOS uncoupling, and deficiencies in antioxidant defense mechanisms, both enzymatic and nonenzymatic, for which we refer to extensive reviews by several groups [54, 56].

In structural kidney disease with normal renal function, such as in proximal tubular cell dysfunction, evidence for increased renal OS with an adequate antioxidant response has been reported, as shown by a study in CLC5-deficient mice, a well-established model of Dent's disease [99]. In the context of progressive kidney disease and CKD however, findings suggest at least the interplay of many different

oxidizing mechanisms, but also decreased antioxidant defense capacities such as the deficiency of SOD, a role for zinc deficiency [55] as well as a decreased activity of the ARE driven enzymes such as HO-1 [115].

In the following section, we summarize briefly what is known for specific oxidative and antioxidative mechanisms in the context of CKD (See also Table 1) in both adults and children. Unfortunately, data in children, especially in predialysis context, are limited.

Mitochondrial dysfunction

In CKD, increased mitochondrial ROS generation and mitochondrial dysfunction are frequently reported. Especially in diabetic nephropathy, mitochondrial dysfunction has been well explored with findings on both morphological as well as functional disturbances in the renal mitochondria [56]. But also in nondiabetic CKD patients, disturbed regulatory MiRNAs such as MiR21 have been reported in CKD patients and an impaired complex IV activity has been reported [57, 59]. Recent evidence also found a role for mitochondrial dysfunction in nondiabetic CKD, more specifically, autosomal dominant polycystic kidney disease, which is further discussed in the accompanying review by Andries et al. in this issue [58, 100].

NADPH oxidases

NOX is induced by different mechanisms. Both in vitro and animal models showed increased NOX4 activity caused by the presence of the uremic toxin indoxyl sulfate (IS), leading to increasing ROS levels [62, 101, 102], and this was also confirmed in CKD patients [66]. *Angiotensin II* is an early key contributor in hypertension and kidney disease progression by the generation of ROS through NOX [65]. Chronic angiotensin II receptor blockade (ATII-R) also improved vascular resistance and decreased OS. ATII-R blockers are considered renoprotective against OS not only by decreasing NOX expression but also by improving eNOS and SOD expression and/or activity [64, 103]. Another cause of NOX-mediated ROS generation in the kidney appears to be *zinc deficiency*, as shown by several groups [63] and discussed in more detail below.

eNOS

In the kidney, eNOS uncoupling was shown to be a major contributor to OS and subsequent renal damage, mediated by different mechanisms: ADMA as well as other uremic toxins have been shown to result in eNOS uncoupling [68, 69]. ADMA is considered a uremic toxin since ADMA levels have been shown to increase in CKD, due to accumulation as well as increased generation by a disturbed PRMT/DDAH activity balance [70, 104]. Recent studies in overweight children showed a significant negative association between plasma nitrosative stress and estimated glomerular filtration rate (eGFR) [105]. In proinflammatory conditions, higher amounts of peroxynitrite can be formed and this can further inhibit eNOS activity. The reduced NO production in the kidney vasculature could result in an imbalance toward higher vasoconstriction and consequent reduction of GFR. In addition, intercellular adhesion molecule-1 (ICAM-1) was significantly increased in obese children and correlated with markers of renal function such as eGFR. Therefore, endothelial dysfunction might be an early step in both cardiovascular disease and renal dysfunction in young people [106].

Myeloperoxidase

Myeloperoxidase has also a well-described role in the development and progression of kidney disease [107]. Recent studies about the link between MPO and renal dysfunction in prepubertal obese children, for example, have shown a positive correlation between 8-iso-PGF2α levels with blood lipids, insulin resistance, and serum MPO levels, with an inverse correlation between both urine 8-isoprostane levels and serum MPO levels and the total antioxidant status. An association between MPO levels and eGFR levels was found as well: Levels of eGFR were significantly increased across tertiles of MPO [71]. This could be explained by the occurrence of glomerular hyperfiltration, initiated by the presence of obesity, which is known to result in glomerular damage and proteinuria.

Xanthine oxidase

In CKD patients, increased XO activity has been shown [73]. If there is a role for XO and/or hyperuricemia on CKD progression remains contradictory. One recent study by Kohagura et al., in 137 patients with hypertension and hyperuricemia who started treatment with XO inhibitors, showed a, albeit modest, protective effect on renal function in hypertensive patients [74].

Superoxide dismutase, catalase, peroxidase, and the GSH antioxidant system

Superoxide dismutasis a key enzyme in the detoxification of free radicals in the cell, and all three isoforms have a high expression in the kidneys [108]. In CKD, an impaired SOD activity has been repeatedly reported [11]. The GSH antioxidant system has been reported as one of the first mechanisms to be disturbed in chronic renal failure [53, 77]. This can also be partially attributed to a Se deficiency [53, 79]. Se deficiency has been reported in CKD and dialysis patients in whole blood and plasma as compared with healthy subjects. This was found at all stages of CKD and dialysis [109]. It has been

associated with increased OS and mortality, albeit mainly from infectious diseases [110, 111]. The exact mechanism between CKD and selenium deficiency is not well known but could also be due to dietary restrictions [78].

ARE-driven enzymes: heme oxygenase-1

Only little data is available regarding the role of HO-1 in CKD patients [80, 112].

Clinical studies confirmed a beneficial effect of the short HO-1 GT_n repeat genotype on cardiovascular outcomes, acute kidney injury as well as outcome of kidney transplantation [113, 114]. In a mouse model of 5/6th nephrectomized mice, Kim et al. found an important deficiency of the Nrf2/ARE-driven enzyme activity despite an increased ROS generation [115]. Induction of HO-1 consequently protected the kidney from ongoing damage [116].

Nonenzymatic antioxidants

Water-soluble antioxidants have generally been reported to be deficient in the context of CKD: CKD patients display hypovitaminosis C which is in their context probably due to dietary restrictions and the use of diuretics [117]. Hypoalbuminemia is a frequently seen feature in CKD patients and can contribute to a decreased antioxidative defense mechanism [85]. Zinc deficiency is repeatedly reported in CKD patients, in adults [118, 119] as well as in children [120, 121].

In contrast to the generally demonstrated normal serum levels of α-tocopherol reported in the CKD population [122, 123], only one group demonstrated lower levels of vitamin E as compared to the general population [11].

Evidence from (pre)clinical studies

Additional evidence can be extrapolated from studies restoring the OS imbalance of kidney disease. Indeed, some interventional studies in humans suggest improvement of renal injury or creatinine clearance with the correction of the OS imbalance [79, 124–127].

As also mentioned before, the renin-angiotensin-aldosterone system (RAAS) blockade is a widely used approach in proteinuric nephropathy and acts through the reduction of renal OS [60, 61, 64, 103].

A recent meta-analysis of the effect of antioxidant supplementation strategies on renal outcome in diabetic kidney disease points toward the beneficial effects with the use of both vitamin E and zinc supplementation on early signs of renal damage. Indeed, zinc supplementation has been shown to significantly decrease renal injury as measured by pathologic changes in animal studies [128] and urinary albumin excretion in both animal and human studies [83, 129]. Unfortunately, these clinical trials mainly include small studies with short-term follow-up. There remains a lack of evidence on hard endpoints such as evolution to ESRD [84]. Another study focusing on renal outcome, performed in patients with type 2 diabetes mellitus and stage 4 CKD, is the BEACON trial, which studied bardoxolone methyl, a Nrf2-inducing agent [130]. The trial design was based upon the findings of the BEAM trial in type 2 diabetes mellitus patients with CKD (eGFR between 20 and 45 ml/min/1.73 m^2), which had shown to improve renal function as measured by an increase of the estimated GFR [131]. This trial, however, was terminated early because of safety concerns, due to an increase in cardiovascular events notably heart failure, nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes in the treatment group [132]. The exact mechanism linking bardoxolone methyl to these cardiovascular events remains unclear. However, the authors suggested that an increase in preload due to volume expansion and an increase in afterload (as reflected by increased blood pressure), coupled with an increase in heart rate, constitute a potentially potent combination of factors that are likely to precipitate heart failure in an at-risk population [132]. This was shown to occur through the modulation of the endothelin pathway, promoting acute sodium and volume [133]. Another explanation for the cardiovascular events resulting from bardoxolone methyl has been provided by Van Laecke et al. They consider the well-known side effect of hypomagnesemia and its association with the risk to develop heart failure with preserved ejection fraction as a potential culprit [134]. Nevertheless, it seems counterintuitive to find cardiovascular events resulting from a HO-1-inducing agent, and it must be acknowledged that bardoxolone methyl is an inducer of Nrf2, a transcription factor that leads to the induction of many pathways and enzymes other than HO-1. Thus, proatherogenic pathways, such as CD36 expression, may be induced as well.

Of note, other antioxidant therapies could also lead to adverse side effects, such as the concern of accumulation of tissue oxalate or gastrointestinal discomforts with high intake of vitamin C. In a meta-analysis of 2012, however, serious adverse events appeared not to be significantly increased [135]. Since mainly small-sized studies have been conducted, however, appropriately powered studies are needed to reliably assess the effects and side effects of antioxidant therapy in people with CKD.

NOX4/1 inhibitors are currently being investigated in diabetic nephropathy. Animal studies showed promising results in different diabetic mice models [19]. The oral Nox1/Nox4 inhibitor (GKT137831) has been evaluated in a phase 2 study assessing a 12-week period of treatment with oral GKT137831 administered in addition to standard of care for patients with type 2 diabetes and albuminuria (https://clinicaltrials.gov/ct2/show/NCT02010242) [19]. Despite promising results in different mouse models of diabetic nephropathy, there was no significant reduction in albuminuria, which was the primary efficacy endpoint of the study. Short treatment periods in advanced

stages of the disease, the effect of stabilization of disease by pretreatment with blockers of the RAAS, and/or a role for other NOXs in human kidney disease might account for the lack of effect on albuminuria in this study.

AST-120, an oral absorbent used particularly to decrease uremic toxins such as IS [124], has been commonly used in Japan to slow deterioration of renal function in patients with CKD. Sato et al. studied in a retrospective analysis of 278 patients, diagnosed with CKD stages III–V, the effect of AST-120 on the need to start dialysis during 5 years. One hundred twenty-eight patients received AST-120 (6 g/day), while the remaining 150 patients did not. The prevalence of dialysis induction, mortality, and cardiovascular events in patients treated with AST-120 was significantly lower after 3 and 5 years compared with the prevalence observed in the untreated patients, suggesting that long-term treatment with AST-120 may improve the prognosis of CKD patients in the predialysis stage [124, 125].

In a small study, Se supplementation has also been shown to improve renal function, as measured by creatinine clearance in 13 stable CKD patients [79].

Other promising, preliminary results on antioxidant therapies include studies with tempol [126, 127, 136], conducted in animal studies: Tempol is a new promising antioxidative nitroxide working as a SOD mimetic. A renoprotective effect of tempol in animal models of hypertension and kidney failure has been reported. The drug not only ameliorated blood pressure through the regulation of NAD(P)H oxidases but also prevented the development of glomerulosclerosis, proteinuria, and the associated loss of renal function [126, 127]. This was confirmed in a 5/6th nephrectomized mouse model where tempol supplementation attenuated OS, inflammation, fibrosis, and deterioration of remnant kidney function [136].

Oxidative stress in CKD-mediated cardiovascular disease

Chronic kidney disease is characterized by a high burden of CVD [137]. Recent data indicate that the impact of renal insufficiency on CVD not only begins with minor renal dysfunction but also appears already at a younger age as compared to the general population [138]. A recent study by Groothoff et al. demonstrated a high burden of CVD in young adults followed with ESRD from childhood onwards [139]. Moreover, it has been demonstrated that the risk of developing CVD in children and young adults with advanced CKD and ESRD is 30 times greater than that of age-matched controls [140]. Therefore, adolescents and young adults with CKD should also be considered at high risk for the development of CVD.

OS has been considered the link between inflammation and CVD in CKD [141]: Several findings in uremic patients point to an imbalance favoring the prooxidative state. Increased ROS activate proinflammatory pathways and eNOS uncoupling initiates endothelial dysfunction, which, in turn, form the first step toward arterial hypertension, arteriosclerosis, and/or heart failure on the one and accelerated atherosclerosis on the other hand [7]. It is generally recognized that both chronic inflammation and oxidative stress play reinforcing key roles in the initiation, propagation, and development of atherosclerosis. In contrast to the data on CKD progression, data on the role of OS in CVD focused not only on surrogate outcomes but also on cardiovascular events and mortality. Interestingly, this does not account only for the CKD but also, at least in part, for the general population with preserved kidney function [27, 142, 143]. Of note, conventional treatments of CVD, including HMGCoA reductase inhibitors (statins), angiotensin-converting enzyme (ACE) inhibitors, and AT1-receptor blockers, are all reported to reduce OS in vasculature thereby improving endothelial function and slowing down CVD progression [144, 145]. However, the use of these drugs is unfortunately not always possible in the CKD population due to side effects or contraindications such as deterioration of renal function and hyperkalemia.

Endothelial dysfunction and arterial hypertension

Undoubtedly, eNOS uncoupling and disturbed NO availability are the major contributors to the increase in cardiovascular disease through the induction of endothelial dysfunction, characterized by decreased vasorelaxation and endothelial cell activation [7]. Several mechanisms have been described: ADMA has been shown to be associated with endothelial dysfunction and vascular disease in CKD [142, 146, 147], but other uremic toxins as well as increased OS itself can cause eNOS uncoupling [148]. Nicotinamide adenine dinucleotide phosphate oxidases are key players as well: Uremic toxins such as IS, homocysteine, and advanced glycation end products (AGEs) increase NOX4 expression and activity, leading to increased levels of OS markers, and endothelial dysfunction in CKD patients [66, 67, 96, 101]. Angiotensin II additionally plays a central role in the pathophysiology of arterial hypertension, as discussed above, through the activation of NOX [65].

In pediatric patients, dysfunctional HDL, which develops at a very early stage in the disease and progresses together with renal function decline, promotes endothelial dysfunction, impairs endothelial repair, and reduces cholesterol efflux [149–151]. Interestingly, elevated amounts of SDMA—but not ADMA—are found in CKD HDL, which indicates that SDMA modifies HDL in order to induce dysfunctional HDL [149]. High density lipoprotein dysfunction is also related to the presence of hypertension, which is one of the most common sequelae of childhood CKD [152]. Indeed, endothelial dysfunction is present in children and young adults with early stage CKD, as reported based on their brachial artery flow-mediated

dilatation [153], which is lower in CKD patients compared to controls [154, 155]. As in adult patients, there is a link between hypertension and left ventricular hypertrophy in pediatric patients [90, 156–158].

MyeloperoxidaseMPO also plays a key role in hypertension and subclinical cardiovascular disease in children, as shown by Correia-Costa et al.: MPO levels associated with increasing levels of 24-h and nighttime blood pressure, together with the loss of dipping pattern. The same study found an independent association between MPO levels and pulse wave velocity (PWV, marker for endothelial dysfunction), which reinforces the hypothesis that MPO is linked with both vascular stiffness and atherogenesis [71].

Arteriosclerosis, arterial stiffness, and left ventricular hypertrophy

Arteriosclerosis is considered a hallmark feature of CKD-related arterial disease and is characterized by progressive concentric media hyperplasia, vascular smooth muscle cell hypertrophy, increased collagen formation, wall thickening, and subsequent calcification [159]. This results in arterial stiffness which translates in increased pulse wave velocity following the cardiac systolic contraction of the heart. The clinical consequences are increased pulse pressure (arterial hypertension), microvascular end-organ damage, impaired diastolic perfusion of the vascular beds, cardiac remodeling (left ventricular hypertrophy), and subsequent risk of malignant arrhythmias [160]. Endothelial dysfunction, inflammation, diabetes, (accelerated) aging, disorders in calcium/phosphorus, and many other conditions contribute to the arteriosclerosis process in CKD [161]. To assess arterial stiffness, carotid-femoral pulse wave velocity is measured [162]. Arterial stiffness and medial vascular calcification are already present in up to 35% of patients with early CKD stages (KDIGO G3–4), and this process already starts in children [163]. A role of oxidative stress in the occurrence of arteriosclerosis and arterial stiffness in CKD has also been reported [164]. Several uremic toxins such as AGEs, IS, and p-cresyl sulfate and eNOS uncoupling have been shown to induce arterial stiffness through increased oxidative stress [165–169]. In a small study, supplementation of L-arginine was shown to be a safe, well-tolerated, and effective way of improving endothelial dysfunction in patients with CKD [169].

Atherosclerosis

There is a well-known role for OS in atherosclerosis [13]. Several mechanisms and markers of OS have been reported as independent predictors of cardiovascular events.

Myeloperoxidase was one of the first enzymes that has been shown to play a causal role in atherosclerosis in both the general as CKD population [26, 27, 72]. Hyperuricemia and XO are linked to both hypertension and atherosclerosis [73, 170]. Increased XO activity was found as an independent predictor of CVD in CKD patients, regardless of uric acid levels [73]. Treatment with allopurinol was associated with improvement of cardiovascular outcomes in a clinical study of 2032 allopurinol-exposed patients and 2032 matched non-exposed patients showing a positive effect of XO inhibition on cardiovascular events [171]. But also nonenzymatic mechanisms are associated with an increased risk for CVD.

Specifically interesting in the context of kidney disease is iron, which can induce the generation of reactive radicals in the presence of peroxides and contribute to lipid peroxidation reactions [172]. Anemia is a common problem among both adults and children with CKD [173]. Intravenous iron supplementation is therefore commonly performed as part of the anemia management both in adult CKD patients [174] and in pediatric CKD patients [175, 176]. It has been shown that iron supplementation induces endothelial dysfunction and generates ROS in CKD patients and accelerating early atherogenesis [75].

Recently, increased ceruloplasmin levels in CKD patients were found to be independently associated with increased risk of long-term adverse cardiovascular events [76]. Several antioxidative losses in CKD have also been associated with increased CVD: Hypoalbuminemia, oxidized thiols [85], and hypovitaminosis C have been reported to contribute to cardiovascular morbidity and mortality [86].

Atherosclerosis is a process that also starts very early in children and young adults with CKD, especially in the ones with one or more risk factors like hypertension, diabetes, hyperlipidemia, and renal disease [92, 177]. In these children, atherosclerosis will continue to progress during life. Carotid intima media layer thickening in predialysis pediatric CKD patients has been reported in several studies [91, 155, 177] and, indeed, significantly correlates with lipid abnormalities and increased oxidative stress in pediatric CKD, which both are risk factors for the development of atherosclerosis [92, 155]. Unlike in adults, no data of possible specific OS-related mechanisms, responsible for atherosclerosis, are found in children and young adults with CKD.

Evidence from interventional studies

Antioxidant supplementation studies have mainly been conducted in hemodialysis (HD) patients, which hampers to assess its efficiency on CKD progression. A reduction in composite cardiovascular events and myocardial infarction has been described in the SPACE study in HD patients with prevalent cardiovascular disease, in whom supplementation with 800 IU/day vitamin E reduced composite cardiovascular

disease endpoints and myocardial infarction [87]. Cocoa flavonol supplementation (CFs) showed promising results in ESRD patients: Rassaf et al. found a sustained attenuation of endothelial dysfunction after the ingestion of CFs (900 mg/day). Moreover, CFs mitigated HD-induced vascular dysfunction and decreased diastolic blood pressure, suggesting amelioration of microvascular function [88]. Similar effects were found by studying polyphenols derived from concentrated red grape juice by Castilla et al. in ESRD patients [178] showing a reduction in oxLDL levels and plasma NOX4 activity. Finally, preliminary findings on zinc supplementation in the context of diabetes also point toward cardioprotective effects in mouse models [84]. These findings certainly underscore indirectly the relevance of the deficient antioxidative capacity in CKD on CVD development.

Conclusion

This review highlights the pivotal role of OS in CKD on both the acceleration of GFR decline and the development of CVD. Many pathophysiological mechanisms, both endogenous and exogenous, lead to (i) increased activity of oxidative enzymes such as NOX, MPO, and XO; (ii) the dysregulation of crucial enzymes leading to mitochondrial dysfunction; and (iii) the phenomenon of eNOS uncoupling or the accumulation of secondary radicals and transition metals, in CKD. In addition, crucial antioxidative mechanisms have been shown to be impaired in adults as well as in children. These disturbances already start in the early phase of CKD, and interventions may help attenuate their deleterious long-term impact. In view of the pleiotropy of disturbed mechanisms, a broad approach will be most probably required. Ongoing research will help clarify the main driving mechanisms underlying the increased OS, their localization, and an integrative approach of both transcriptional and signaling pathways within the context of CKD. Many promising approaches are currently investigated. Especially in the field of pediatric medicine, dietary interventions and endogenous antioxidant supplementation should be considered as attractive beneficial approaches given their low burden of accompanying side effects.

Funding information DM is supported by the Clinical Research Fund of UZ Leuven, by the Fund for Scientific Research G0B1313N, and by a research grant from the European Society for Pediatric Nephrology. FJ is a Fellow of the Fonds National de la Recherche Scientifique.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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